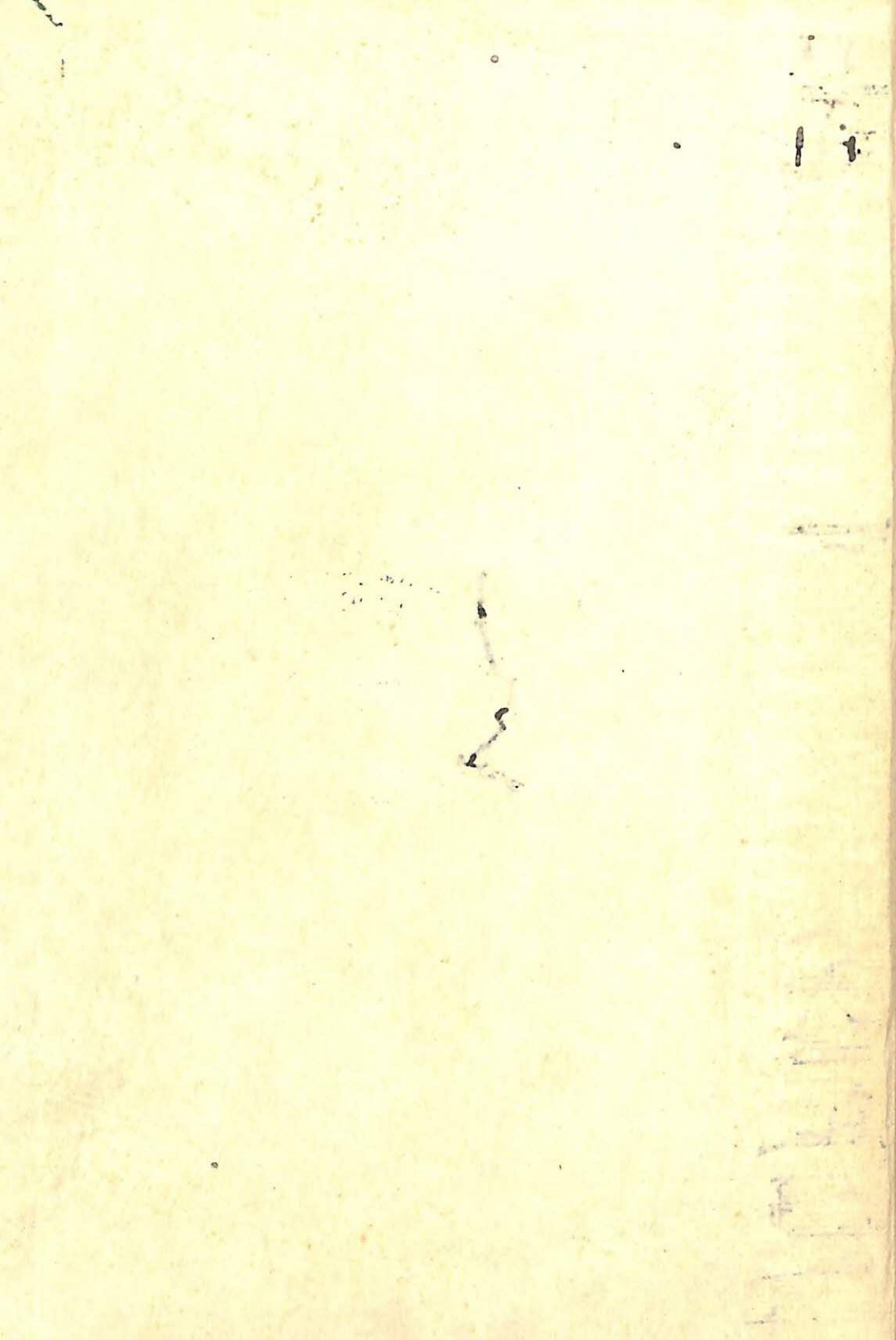
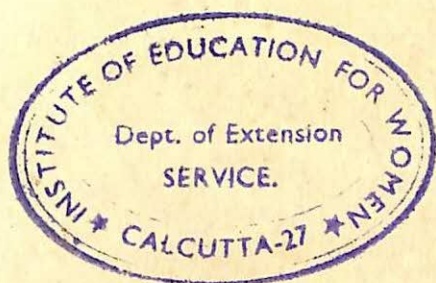


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GENES
AND THE
MAN
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GLASS





THE SCIENCE IN MODERN LIVING SERIES
Basic Science Material for Use in Modern Education

BUREAU OF EDUCATIONAL RESEARCH IN SCIENCE

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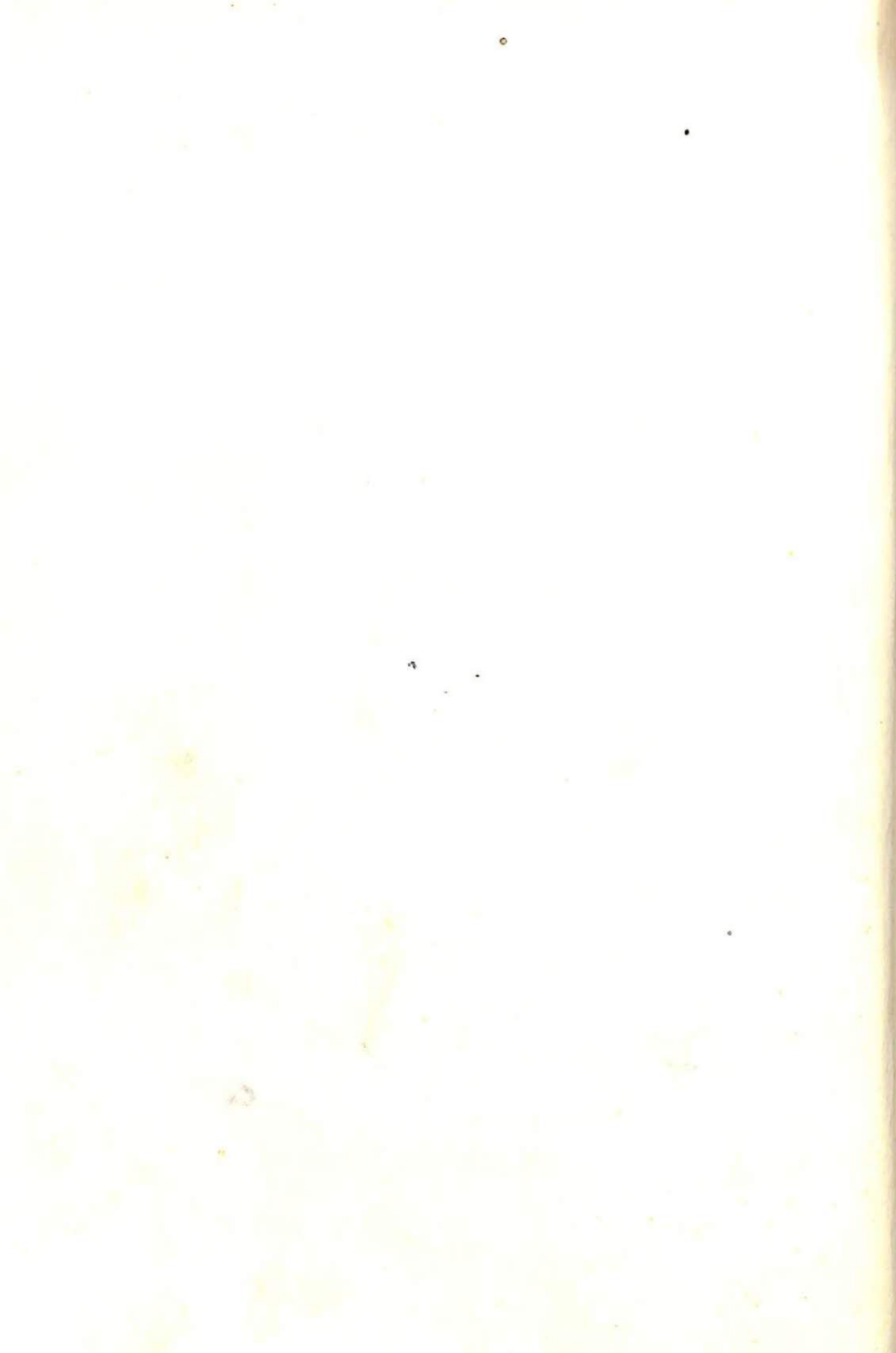
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Genes and the Man

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Editor's Foreword

As the fifth volume in this series of basic science materials, *Genes and the Man* attempts to integrate the fields of reproduction, genetics, and growth and development as they relate to human life. To understand an individual, whether animal or plant, we need to know how the hereditary pattern is formed at reproduction and how it reacts with environmental factors as growth and development of an organism take place. The course of development presents features which we can interpret only in the light of our racial past or in terms of the individual's future needs. Therefore, the material here has been selected for its contribution toward building a conception of the individual as an organism continuously growing and developing along lines laid down by the hereditary pattern but modifiable by external circumstances.

Even though life begins with a hereditary pattern, we must realize that the interaction of this pattern with its environment determines the growth and development of the individual. On education devolves the guidance of development after the uniform environment of our prenatal days is replaced by a constantly changing and widely diverse one. Genes alone do not make the man.

The author of this volume, Bentley Glass, is a successful teacher of biology and a fruit-fly geneticist. As a teacher he is at the same time a student of human relationships and has endeavored to apply the theory and the findings of his research

to the much broader and more difficult field of human genetics.

The timeliness of its content because of its bearing upon current discussions of cultural conflict in relation to the hereditary nature of man makes the book of interest to laymen as well as educators. However, it is designed primarily to increase the effectiveness with which educators serve society through the young people placed in their charge.

SAMUEL RALPH POWERS

Preface

THERE are several textbooks on genetics, and it has not been my intention to add to their number. Rather, I have hoped to fill a gap of another kind. It appears to me important that we should conceive of human life in genetic terms, that we should understand the epic sweep of an individual's growth and development up to maturity and the long years of slow decline thereafter, together with those tenuous physical bonds that link each generation with all before and after—that we should understand these, I repeat—by tracing them from their beginnings in protoplasm and the genes. Physiologists, dealing with perfected structures and functions, and geneticists, occupied with the behavior of chromosomes, have both been somewhat isolated from the embryologists. No doubt, this condition has existed because of the highly specialized training necessary for a scientist to do fruitful work. Yet life is a whole. The genes and the chromosomes are important to us only because of the effects they produce during the course of growth and development; and the completed man is fully intelligible only as we perceive what has made him as he is. It is a startling fact that this theme, which surely ought to form the core of our teaching of general biology, is commonly relegated to the rarefied zone inhabited solely by the specialist student of zoology.

Throughout the realm of science the narrow, rigid boundaries of specialized fields of subject matter are at last break-

ing down. The boundary between genetics and cytology has already disappeared, and it is now evident that embryology and physiology are beginning to enter the amalgam. As yet, however, this trend is apparent only in the more technical studies. In general education, compartmentalized biology continues to gain ground. For these reasons this volume has been prepared to indicate a new outlook, not to present genetics, or cytology, or embryology, or physiology, or even a summary of all of them, but rather to describe the operation and interaction of those factors which make the physical man, insofar as we know them or can reason about them today.

This purpose may explain some features of the book that at first sight appear strange, such as the gaps in the treatment of his field that will strike the geneticist. Because the central theme is that of man's growth and development, plants are introduced only casually to indicate the universality of such phenomena as cell division and meiosis.

To some extent, the relative proportions of the sections of the book have been determined by the availability of good general discussions of their subjects. Cell division (Chapter I) and the genetic basis of sex (Chapter III) have been treated at considerable length because of the general inadequacy of discussions of these subjects, while the treatment of the mechanism of heredity, available in many excellent accounts, is here greatly condensed. The present account starts with the single cell which each of us once was, and examines the conditions of its growth and reproduction. The next two chapters provide the historical setting for that cell, tracing its continuity with the earlier generation of cells and of beings that have provided its heritage. Next follows an analysis of the nature of development, a study of the complex interactions of gene with gene, of genes with cytoplasm, of organic part with part, of whole with part, and of all these with the various aspects of their environment. Finally comes a descriptive account of development, culminating in maturity and sinking at last into senility and death. With each man there

perishes the unique assemblage of genes that along with the ever-varying environment made him what he was. But the genes themselves, cast into new arrays in the reproductive cells, are as immortal as life itself.

ACKNOWLEDGMENTS

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In no case, of course, should any of these individuals be held responsible for the final expression of fact or opinion, which was determined by the author alone.

BENTLEY GLASS

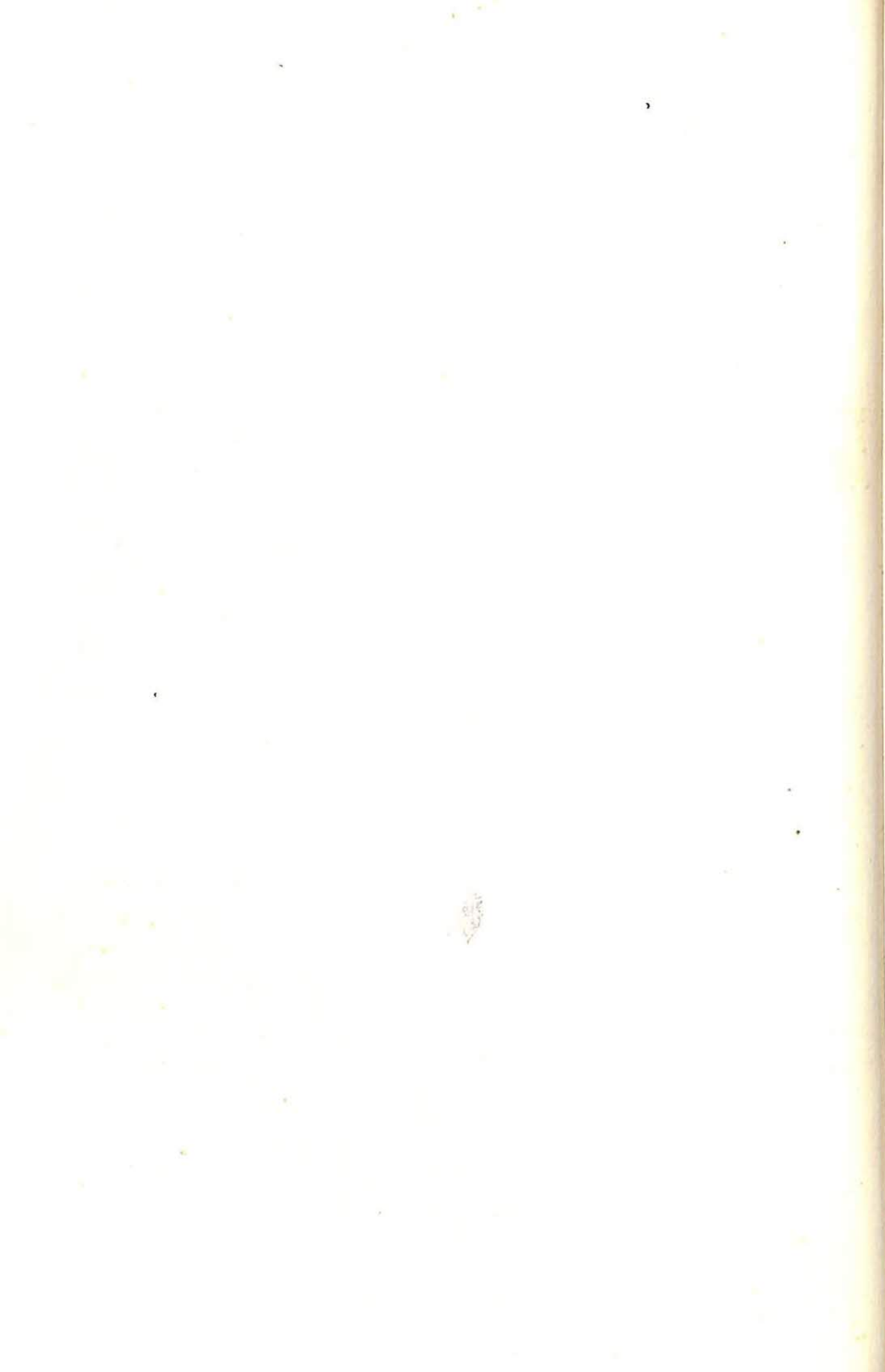
Baltimore, December 15, 1942

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Genes and the Man





CHAPTER I

Life Begins—The Single Cell

TO understand a man, we must know as much as possible of his past life. Today's actions and attitudes are rooted in early training; our childhood conceptions and beliefs, fashioned according to the pattern of our culture, persist in our adult behavior. This we all know. On the other hand, how few of us comprehend the nature of those fascinating processes of growth and development which lie back of our first conscious memories. Yet without this knowledge we can no more understand ourselves as we are today than we can comprehend the nature of our society and government without knowing something of the story of the settling of America, the Revolution, the Civil War, and the expanding frontier.

The mold of our social life is set ere we come on the scene; we may conform or rebel. However, it seems more intelligent to learn what this mold is in the light of how it came to be. For, though set, it is not unalterable; slowly in good times, often swiftly in evil, it can be changed by the pressure of circumstance; and understanding, we may play our part. So it is with our individual growth and development, too. From our parents we receive a hereditary pattern which largely determines our physical and mental nature, and which in the course of its realization is modified by whatever situations we meet. *Every characteristic of an individual can result only from the interaction of hereditary*

and environmental factors. The physical basis of our heredity is, indeed, determined from our life's beginning, but from that moment on our surroundings continuously exert their influence, sometimes strongly, sometimes with little effect. The interplay of these contrasting factors is evident at every stage in the emergence of a man or a woman.

As an individual develops, features appear which we can interpret only in the light of the past of our kind. Besides this, development commonly proceeds as though future needs were anticipated. As an embryo obviously can neither foresee its needs nor remember human history, such facts must mean that the racial pattern of heredity has itself been adapted to these needs, and very well adapted at that.

Let us aim, therefore, to trace the interaction of the hereditary pattern with the environment throughout the mounting complexities of growth and development, and, moreover, to interpret it in terms of our racial past and the goal of mature fitness for the needs and activities of life. To unravel these myriad twisted and tangled threads, however, we must find their beginnings. What is the nature of an individual at the moment when his life begins? We can answer this only if we know in turn how an individual comes into existence. Our course must be first to treat the origin of the individual; next, his preformed nature, a matter of hereditary pattern. Only thereafter can we begin to describe and analyze the actual processes of growth and development.

SPONTANEOUS GENERATION MAY EXIST IN THE BORDERLAND
BETWEEN THE LIVING AND THE INANIMATE, BUT IT OCCURS
NO HIGHER IN THE SCALE OF LIFE

Only in modern times has there come a realization that all individuals originate from previously existing individuals of the same general kind. The ancients, including even Aristotle, commonly believed that the lower forms of life, especially parasites and "vermin," sprang from slime or

putrefying matter. (See Note A, p. 48.) The idea that such living forms might generate spontaneously was not even challenged until the seventeenth century, and for two hundred years thereafter men's ideas on this matter seemed to depend chiefly upon whether they were religious or materialistic, or upon whether they leaned to one or another theory of reproduction and development. (See Note B, p. 49.)

It was not until our North and South were locked in civil war that Pasteur and Tyndall performed the experiments which showed that even the minutest living organisms, the bacteria which are associated with processes of putrefaction in nutrient fluids, are not formed spontaneously from inanimate matter. Like dust, these organisms float in moving air, settling slowly whenever the air becomes still. If they chance to fall into a solution furnishing an abundant food supply, each germ can, in a few hours, produce hundreds of millions of its kind. But if the air to which such solutions are exposed has been completely still so long that all dust and bacteria have settled, or if the air is filtered through cotton plugs, no bacteria can reach the fluids. By boiling the nutrient solutions after the containers have been plugged or by bending the open necks so that no germs can enter, putrefaction can be prevented indefinitely. (See Note C, p. 50.)

Probably no experiment has had greater effect upon the welfare of mankind than this one! It has made possible the isolation and study of individual types of germs, and the elucidation of their relationship to disease; upon it modern bacteriology and medicine are founded. It has made possible the preservation of sterile conditions during operations, and thus surgery has been relieved of its once frightful aftermath of infection and death. Besides, when it was found that boiling the fluids was unnecessary and that heating to 60° - 65° C. for 20 to 30 minutes was sufficient to destroy nearly all the germs, particularly those causing disease, a method was available for the treatment of milk which removes most of the

bacteria without greatly altering its nutritive qualities. To this "pasteurization" method, now legally enforced in many cities, we owe much of the great drop in infant mortality which has characterized the last five decades in Europe and the Americas. Countless thousands of babies once died of typhoid and other milk-borne diseases in their first year; now, fortunately, there is little danger from this source.

Still, there were at first troublesome exceptions to the efficacy of these methods. Adherents of spontaneous generation took new heart, for occasionally even the most carefully plugged and heated solutions putrefied. Alas for their views, further study soon led to the discovery that certain microorganisms form very tough, resistant *spores*, able to withstand great heat and afterward to germinate. To kill these and so to obtain perfectly sterile solutions, it is necessary only to reheat the solutions after the spores have had a chance to germinate. Accordingly, pasteurization was modified to include two heat treatments separated by an interval of hours—a method now standard practice in canning foods.

Pasteur¹ and others thus demonstrated to us that the living forms with which we are acquainted are not arising spontaneously under conditions existing on the earth today. On the other hand, all indications point to the former presence upon the earth of conditions under which life as we know it simply could not have existed. At some time or other, then—perhaps more than once—life must have originated here.²

¹ The efforts made by Pasteur to remove all possibility of belief in spontaneous generation are recounted in the glowing tribute by his son-in-law, René Valléry-Radot. This life is one which should be read and reread by all even remotely interested in biology. (Valléry-Radot, R. *The Life of Pasteur*, Eng. trans. Doubleday, Page, New York, 1916.)

² We shall pass over those theories which hold that life has come to the earth in the form of spores floating through space, since they merely remove our problem to another sphere. Life as we know it clearly depends for its existence upon such a concurrence of natural factors as is found on the earth today. (See P. B. Sears, *Life and Environment*. Bureau of Publications, Teachers College, Columbia University, New York, 1939.) Not only have we no indication of the existence of such a situation elsewhere, but even were there such a place, we should still have no notion of how life might have originated there any more readily than here.

Is there any evidence as to how the chasm between the lifeless and the living could have been bridged?

The bacteriophages and filtrable viruses³ seem indeed to stand in such a position. Until recently they have been regarded by everyone as living. Like the parasitic bacteria, they multiply within the tissues of a particular plant or animal host, setting up specific disease conditions and stimulating extremely specific and lasting immunities. When they are exposed to x-rays, they are inactivated; the doses required to do this correspond closely to those which kill bacteria or spermatozoa. They are so small as to lie beyond the utmost power of our best microscopes, making it impossible for us to observe them individually, but their behavior is biologically just like that of the bacteria.

On the other hand, there is mounting evidence to show that the bacteriophages and filtrable viruses are not alive. Instead of being a complex colloidal system, like protoplasm, at least some of them are single chemical molecules. This, of course, has long been indicated by their size, for while some almost reach the limit of microscopic visibility ($200\text{ m}\mu$), others, such as the virus of infantile paralysis, are no larger than some of the protein molecules ($10\text{ m}\mu$). The evidence as to their molecular nature now seems conclusive. Dr. W. M. Stanley, of the Rockefeller Institute, and his collaborators have succeeded in isolating, by two quite different methods (chemical extraction and ultracentrifuging),⁴ the virus that causes the tobacco mosaic disease. This virus proves to be a

³ Bacteriophages prey upon specific bacteria, dissolving their colonies, while filtrable viruses produce such plant diseases as tobacco mosaic disease, tobacco ring spot, potato leaf roll, and peach yellows, and such animal and human diseases as measles, mumps, infantile paralysis, smallpox, rabies, yellow fever, typhus, fever blisters, and shingles.

⁴ The ultracentrifuge is a high-speed centrifuge, capable of rotating materials at upward of 60,000 revolutions per minute, and of developing a force well over 100,000 times that of gravity. Such forces will separate the component phases of a suspension or emulsion into layers (stratification), with the heaviest layer at the "bottom" and, in the order of their specific gravities (relative weights in comparison with that of an equal volume of water), the lighter layers above.

protein crystal, of the greatest molecular size known (molecular weight about 43,000,000). The crystals have lost none of the power of the original virus to produce the disease when inoculated into tobacco leaves; in fact, they *are* the virus.⁵ Other plant viruses and animal viruses have also been isolated by the ultracentrifuge, and they, too, turn out to be protein crystalline substances of huge molecular size. With the successful development of the electron microscope, the tobacco mosaic virus has been photographed. It appears to be a slender rodlike crystal, 280 $m\mu$ in length and 15 $m\mu$ in each of its two other dimensions. Even the virus of influenza A, which is among the smallest of all known viruses, having a diameter of only 11 $m\mu$ and a nearly spherical shape, has had its picture taken.

Here are substances which, because they are monomolecular and crystalline, may well be classed as nonliving, but which behave like living organisms in a number of ways. It is not incredible that our knowledge of the chemical synthesis of organic compounds may continue to advance until viruses can be produced in the laboratory just as various vitamins and hormones are already being produced. Would this be the artificial production of *life*? And would our success make the occurrence of spontaneous generation seem any more probable?

To understand what we are asking, we must raise once again the old question that has ever baffled man's persistent curiosity: What is "life"? What makes a thing "alive"? Can we at last begin to discern an answer? Life, perhaps, is not any one thing. It is a group of attributes, no doubt assembled one by one, which we constantly associate because we are most familiar with systems (plants and animals) in which they occur together. Yet any one of these can be found by itself in some nonliving system. If, then, by the spontaneous

⁵ For the proof of this point, Dr. Stanley received, in 1936, the prize of \$1000 awarded annually by the American Association for the Advancement of Science for an especially outstanding paper among those presented at its Christmas session.

generation of life we mean the simultaneous concurrence of all these attributes, the experiments of Pasteur answer us emphatically: No! But if we mean the emergence of any single characteristic, selected as of primary importance, may not the answer be different?

Not least important among the attributes of life is the ability of a particular chemical molecule or group of molecules to duplicate itself repeatedly, a property which is known as *autocatalysis*. This multiplication can take place only under narrowly specific conditions. The raw materials needed for the synthesis must be present in the environment, and physical conditions must be appropriate. Certain enzymes perhaps have this ability, and certainly the 'phages and viruses do; in other words, it is an ability that may be possessed by "nonliving" systems. Yet, as we shall see, this property of life is the very basis of reproduction. Remembering that individuals arise only through reproduction—that from generation to generation life is a continuum—one is tempted to say: Surely *this* is the basic attribute of life! Then, is not the chasm between living and nonliving bridged? Whatever our answer, at least our attention is directed forcefully to the nature of the reproductive processes.

CELLS ARE FORMED BY THE DIVISION OF PRE-EXISTING
CELLS, A DIVISION ESSENTIALLY A TRANSMISSION OF THE
REQUISITES FOR CELL GROWTH AND DEVELOPMENT

Although the theory that all plants and animals are composed of units called *cells* was proposed in 1838–1839, it was some time before there was any very good idea of how cells are formed.⁶ By 1855, however, Virchow was able to sum up

⁶ Actually, although Schleiden and Schwann have been almost universally credited as founders of the cell theory, others, notably Mirbel, Lamarck, Dutrochet, and Turpin, had expressed virtually the same ideas considerably earlier. It was merely the vigor with which Schleiden and Schwann advocated their views that marks the years 1838–1839 as the beginning of a new era in biological thought. As to their views on cell formation, they had most curious and erroneous ideas. Schwann, for example, believed that new cells

many observations on the origin of cells by means of the division of preëxisting cells in the dictum: "Where a cell exists there must have been a preëxisting cell, just as the animal arises only from an animal and the plant only from a plant."⁷ "It is here that the full significance of the cell-theory for heredity and development first dawns upon us. If the cells of the body always arise by division of preëxisting cells, all must be descended by division from the original germ-cell as their common ancestor; and such is the observed fact. . . . This critical point once made clear, the dominating significance of cell-division in the history of life began to stand forth in its true proportions." Cell division in an individual's development "is but an infinitesimal part of a greater series of cell-divisions that has no assignable limits in the past or future. *The germ-cell arises by division of a cell preëxisting in the body of the parent, and in its turn divides to form the body of the offspring* [italics added by author] and also new germ-cells for coming generations; and so on without end. Embryologists thus arrived at the conception . . . of an unbroken series of cell-divisions that extends backwards from our own day throughout the entire past history of life. So far as we know, life under existing conditions never arises *de novo*. It is a *continuum*, a never-ending

usually arise by a sort of "crystallization" from a "formless moisture." For a recent consideration of the origins of the cell theory, see the paper "Cell and Protoplasm Concepts: Historical Account" by E. G. Conklin in *The Cell and Protoplasm* (American Association for the Advancement of Science, Science Press, Lancaster, Pa., 1940).

⁷ The German pathologist, Rudolph von Virchow (1821-1902), was convinced that only through knowledge of the nature of the cell could light be thrown upon disease. This idea was lost sight of during the period when diseases were being traced to germs. Virchow himself bitterly opposed the advances made by the bacteriologists, and ended by dropping this work entirely and turning to archaeology and anthropology. Today medical men are beginning to realize that even where the specific external cause of a disease is known, they have grasped only one aspect of it. What the germ does to the cell, and what the cell does to defend itself, are just as vitally important. Here we have a good example of the way in which many scientific ideas, born ahead of their time, eventually come into their own. The quoted sentence in the text is from Virchow's *Cellularpathologie*, p. 25 (1858).

stream of protoplasm in the form of cells, maintained by assimilation, growth and division. The individual is but a passing eddy in the flow which vanishes and leaves no trace, while the general stream of life goes forwards.”⁸

Since this unbroken series of cell divisions links generation to generation, and a cell from the body of a parent divides to form the body of the offspring, all requisites for growth and development must be components of the cell. *Reproduction is therefore essentially a contribution of these requisites by the parent cell to its cell offspring.* What are the requisites? There must be, first, a complete set of those factors which control the specific composition and organization of living substance and the characteristic course of events in all the processes underlying growth and development; and second, a supply of the organized living substance capable of carrying on all essential activities, and often including certain specialized derivatives and a supply of food sufficient to maintain the organism until it is itself capable of securing more—that is, first, *genes* and second, *protoplasm*.⁹

⁸ Wilson, E. B. *The Cell in Development and Heredity*, ed. 3, pp. 9-11 (Macmillan, New York, 1925). The introduction to this great biological classic is superlative writing. Chapters IX, XI, and XII provide material on cell division, the individuality of the chromosomes, and their relation to heredity, which may well be consulted in connection with the present discussion.

⁹ It is true that in general usage *protoplasm*, no doubt, includes also the genes, but in the absence of a word to designate extragenic protoplasm the present usage may be allowed.

Living protoplasm is a complex system, perhaps best described as a *colloidal sol*, that is, a mixture of dispersed ultramicroscopic particles suspended in a fluid. In protoplasm the particles are chiefly protein and the fluid is a watery solution of various salts, sugars, and other soluble substances. The colloidal sol is capable of a reversible change into a *gel*, in which the solid portion, or phase, of the system becomes a continuous meshwork, while the fluid phase may either be broken up into separate droplets or remain continuous. In protoplasm the solid phase itself has a strong affinity for the fluid phase, so that the gel can vary enormously in its fluid content and is highly elastic. The change from a sol to a gel is gradual, and is most apparent in the alteration of the *viscosity* (resistance to flow) of the mixture. Many important life activities appear to depend upon localized changes in viscosity within the cell, e. g., the locomotion of ameboid cells and the mechanics of mitosis (see pp. 35-37). Sol-gel reversibility is therefore of fundamental biological importance. External factors which affect it, such

(plus foodstuffs, and so forth). Reproduction deals with the transfer of these essentials.

What evidence have we that both of these classes of substances are requisite? A very good indication that genes alone cannot survive and grow comes from the fate of the spermatozoon. Each sperm is made up of little more than a single tightly packed set of genes. Spermatozoa, however, are incapable of continued life, and die as soon as their stored supply of energy-yielding substances is exhausted. The spermatozoon that penetrates and fertilizes an egg, however, as we shall see, absorbs substances and contributes its share to the control of growth and development. Like sperms, the tiny polar bodies thrown off by an egg (see p. 132) are incapable of further development alone. Like the egg, they have a complete single set of genes, but they possess only a very small amount of active protoplasm and practically no stored food. Without protoplasm and foodstuffs genes must perish!

But, an abundant supply of protoplasm and foodstuffs is apparently of no avail if the genes are absent. A geneless fragment of a cell usually succumbs quickly; in any event cells lacking genes, such as the red blood cells of mammals, can survive for a limited period only and cannot reproduce. As a rule, one set of genes seems sufficient to promote normal development, although with increasing sets there often goes an increase in size of both cell and organism. But in the higher organisms, the absence of any representative of even a single gene generally results in death or enfeeblement. It appears true that *practically every gene native to an organism is essential to normal functioning for every one of its cells*. Even an unbalance in the normal make-up of the gene complex is very injurious. Let but a few genes be present in more or less than their normal proportion and there may be a marked deleterious effect upon the individual. The battery of genes in an organism is a delicately adjusted system, the

as temperature, hydrogen ion concentration (pH), and mechanical agitation (shaking and stirring), are consequently important too.

parts of which are tuned to harmony with one another. One may double or triple the system without changing its balance, just as one may multiply both sides of an equation by the same factor without altering their equality; but one cannot add to or subtract from one side and not treat the other similarly without destroying the balance of the equation.

Heredity results from the genetic continuity of dividing cells

This idea August Weismann strenuously reiterated, until at last he ran the danger of carrying it too far. The fundamental effects of the principle are, nevertheless, quite clear. No child inherits its characteristics from its parents' bodies (soma), but from their germ cells, and each of these in turn has descended in unbroken lineage from that one original cell, the fertilized egg or *zygote*, which by division gave rise to all the cells, somatic and germinal, of that parent. Therefore nothing that happens to the parent's body can be inherited, unless in some way the effect can be passed on to the germ cells, and these through their internal situation are usually well protected from external influences. To be sure, certain effects, such as those of alcohol or a change in climate, may reach them. However, in the course of time these effects wear off, although it may take a number of generations. Only changes of the genes are known to be truly lasting, in a strict sense hereditary. So far as we know—and just about every imaginable way has been tried—*genes cannot be affected indirectly*. This fact shatters all theories of the inheritance of acquired characters. No parent should hope that his own education, or fear that his lack of it, can have the slightest effect upon the native intelligence of his offspring. No biologist can very consistently believe in the evolution of living organisms through any effort on their part to meet their needs or to satisfy their wants.¹⁰

¹⁰ This subject is discussed with unusual clarity in Chap. XV of H. S. Jennings' well-known book, *The Biological Basis of Human Nature*, pp. 329-358 (W. W. Norton, New York, 1930).

Since there are many vitally necessary genes per cell, as we have indicated, the process of transmission must involve a duplication and a distribution of each one. *The basic reproductive process is therefore that which brings about the qualitatively equal distribution of the genes.* Now where are the genes? Clearly we must hunt for them in some qualitative phase of cell division, that is, some phase which would distribute to each of the cell offspring identical sets of bodies.

Knowledge of the actual mechanics of cell division followed a great development of the technical side of biology. Methods of killing, fixing, sectioning, and staining tissues made possible the accurate observation of cellular form and structure. A group of brilliant men in the thirty years from 1870 to 1900 formulated our ideas of the physical basis of heredity and the mechanism of development. They observed carefully; they preferred sound reasoning to speculation; and important advances came thick and fast. Observing animal eggs, Fol was the first to see the rays that appear in the protoplasm at opposite sides of the nuclear vesicle, making the star-shaped figures he called *asters*; and Bütschli observed that, as the nuclear membrane disappeared, the rays stretched across it to form a spindle-shaped figure between the asters. In a plane through the middle of the *spindle* lay small grains or tiny rods, now known as *chromosomes* because they stain intensely. These were seen to split into two groups that moved toward opposite ends of the spindle, where, according to Oskar Hertwig, each is reconstructed into a typical nucleus. Strasburger extended the observation of these phenomena to plants, finding essentially the same behavior, except for the lack of asters. He made an additional discovery when he showed that before the spindle is formed the chromosomes are to be seen in the nucleus as long, twisted double threads, which later shorten and thicken. This was confirmed for animal cells by Flemming, who also showed that the double strands come from a *lengthwise* splitting of each chromosome. The culmination of this series of researches

was reached when van Beneden demonstrated that the chromosome halves, after being arranged upon the spindle, separate, one strand of each chromosome passing to each pole.

Division of the cells is completed by furrows which appear in the equatorial plane and deepen until the cells are completely separated. In plants, however, a plate forms in this position, thickens, and becomes the dividing cell wall. Thus the cell substance surrounding the disintegrating spindle, with all the globules and grains of food suspended in it, is divided between the daughter cells. This division may be equal or very disproportionate, depending upon physical mechanisms which will be examined later. Evidently a gross quantitative division of the protoplasm is sufficient.

To the group of men who worked out the nature of cell division—Fol, Bütschli, Oskar Hertwig, Strasburger, Flemming, and van Beneden—and to others who, through technical advances, made their work possible, or who confirmed and extended their observations to hundreds of plants and animals, we owe a discovery which deserves to rank in importance with those other great biological discoveries of their day: Pasteur's discovery of the causation of disease by bacteria, Mendel's discovery of the basic laws of heredity, and Darwin's epochal enunciation of natural selection as a basis of evolution. How often while honoring such a lone genius as Mendel we forget others whose cooperative and cumulative labors have proved no less outstanding, men like these whose discovery of the mode of cell division is fundamental to our understanding of reproduction, heredity, growth, and development.¹¹

As this process of chromosome division and distribution, which was named *mitosis*, proved to be of nearly universal occurrence, the significance of a division that is qualitatively, rather than quantitatively, equal was perceived. What sub-

¹¹ See E. Nordenskiöld, *The History of Biology*, Eng. trans., Knopf, New York, 1928, Tudor, New York, 1935; and W. A. Locy, *Biology and Its Makers*, ed. 3, Holt, New York, 1915. Nordenskiöld is more scholarly, but Locy's book is better illustrated.

stance, except that carrying the hereditary properties, asked Roux, the father of experimental embryology, and Hertwig and Strasburger, could be of such importance as to require so meticulously equal a distribution?

The chromosomes have persistent individuality

There remained one great objection to assigning to the chromosomes leading roles in the drama of heredity. They vanish! At the close of each mitotic division, they disappear from view, and during the relatively long "interphase," lasting until the beginning of the next division, only isolated granules of their component chromatin are visible in the stained nucleus. The demonstration that chromosomes persist from one cell generation to the next, whether lost to view or not, is primarily due to the long continued research of Boveri. He succeeded in showing that *the number of chromosomes reappearing after the interphase is regularly the same as the number of chromosomes disappearing at its beginning*. In *Ascaris*, for instance, if the two chromosomes of the egg become separated, they will form two small nuclei instead of a single larger one, and after the interphase one chromosome will reappear in each. In other forms, both plant and animal, it has been shown repeatedly that whenever the chromosome number becomes accidentally altered the new number persists indefinitely.

A broader aspect of this same principle is the constant number of the chromosomes in the cells of a particular race. Each form of life investigated, whether plant or animal, has been found to have a characteristic number of chromosomes in each cell nucleus, a number ranging from two (in *Ascaris megalocephala*, the horse roundworm) to 200-208 (in various species of the crayfish, *Cambarus*). In man the number is forty-eight. In two animals, a bug and a mite, the characteristic number has been traced through every stage of development and into every tissue.¹²

¹² Too much importance, however, should not be attached to these numbers. Closely related forms often have very different numbers, while the same num-

Another type of evidence is also very significant. In *Ascaris* the chromosomes are very long and their tips project in lobes from the surface of the nucleus. These lobes persist during the interphase, and when the chromosomes reappear their ends project into them just as before. In a certain grasshopper the chromosomes also form separate lobes, while one of them retains its identity even further, forming a separate nucleus pressed against the larger one. In certain cells of a minnow (*Fundulus*) and a snail (*Crepidula*) the chromosomes never fuse completely, but each forms essentially a separate nucleus during interphase.¹³

Most striking of all is the case of a protozoan described by Bělař. Here cell divisions succeed one another so rapidly that before the enormously long chromosomes have been fully separated to their "tails," their "heads" begin to take

ber occurs in widely different species. Thus a snail, an ant, various rodents, and several plants as diverse as a brown alga and members of the banana, lily, crowfoot, violet, and composite families share the chromosome number of man, while among the rats and mice we find such a variety as 40, 42, 48, 50, 52, and 54. The honeybee is another sort of exception, as males have 16 chromosomes and females 32. (See Chap. III, p. 129.)

The basic chromosome number may also be multiplied in single cells or in tissues within one individual. This multiplication may take place through fragmentation of large chromosomes into tiny ones, a condition which occurs in *Ascaris*, where the two chromosomes found in the germ cells separate into about sixty in somatic tissues. (Conversely, two or more chromosomes may combine and act, either for a time or permanently, as a unit.) Still more common is doubling due to the division of the chromosomes without an accompanying division of either nucleus or cytoplasm, so that all the daughter chromosomes remain in one nucleus within one cell. This is especially frequent in cells that are old and highly specialized. In a number of species of fruit fly (*Drosophila*), for example, the number of chromosomes in the tracheal cells is regularly double the usual somatic number, and in the rectal glands the number is redoubled. Doubling may be brought about by exposure to cold or chemical agents during mitosis, and it is notably abundant in degenerating cells. In mosquito pupae, intestinal cells degenerating during metamorphosis have been seen with 6, 9, 12, 18, 24, 36, and 72 chromosomes, where the characteristic number is 12. Cells of cancerous tissue often have giant nuclei, or several nuclei in each cell, due to a similar duplication of the chromosomes without cell division.

¹³ This condition also occurs in a strain of maize. Here it is known to be due to the action of a single gene, a first instance of the control of the genes themselves over the character and behavior of the chromosomes.

part in a subsequent division. The chromosomes being separated on the spindles of the secondary divisions are still associated for most of their length, and at their farther ends are still entwined with their duplicates in the sister cell (see Fig. 1). As there is an interphase between these divisions, *the very association compels us to see a morphological continuity of the chromosomes through the interphase.*

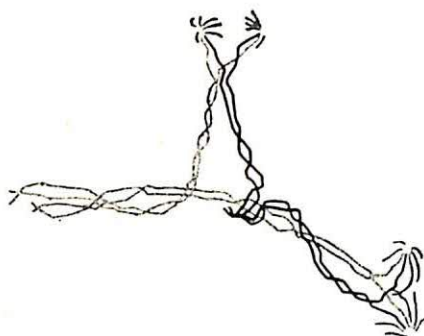


FIG. 1. Two pairs of enormously long chromosomes in the protozoan *Aggregata eberthi* involved in two cell divisions at once. Their "heads" are passing through a second cell division before their "tails" are completely separated after the first division. (Redrawn after Bélař)

The persistent individuality of the chromosomes is also shown in the way in which differences in their size and form are passed on from cell generation to cell generation, being transmitted regularly and characteristically to each of the cells of the organism, and on to successive generations of individuals. Chromosomes vary principally in length. They are, as a rule, globules or rods or shaped like V's or J's. Constancy in their size and form has now been observed in a very great number of plants and animals.

Unusual types, such as the bent-tipped chromosome found in a certain locust, have also persisted in cell generation after cell generation. In 1922 some female fruit flies were discovered in which two rod-shaped chromosomes had become attached to each other at one end, forming a V. This stock (called *attached-X*) has been widely used by geneticists all

over the world, and the new chromosome has now persisted for more than 500 generations.

When chromosomes are exposed to x-rays, they may be broken and reconstructed in various ways. If a piece is broken out of the middle of a chromosome, or off its end, it may be visibly shortened, depending upon the size of the lost piece. When two chromosomes break simultaneously, pieces are frequently interchanged; and if these are not of the same size, the chromosomes are altered in size and shape (Fig. 2). These chromosomal abnormalities are all *perma-*

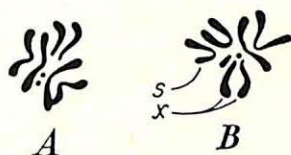


FIG. 2. *A*, the normal chromosomes of the female fruit fly (*Drosophila melanogaster*). (From Mohr) *B*, chromosomes of the female *Drosophila* following breakage and reconstruction. One of the longer V-shaped chromosomes (*S*) has lost a piece that has become attached to one of the small globular chromosomes. The chromosomes marked *X* are those that determine the sex of the individual. (From Dobzhansky)

nent, and are transmitted from parent to offspring, from cell to cell.

In the salivary gland cells of flies the individuality of the chromosomes is demonstrated to the highest degree. Here are giant chromosomes, thousands of times greater in volume than those in ordinary somatic or germinal cells, which can yet be identified with the tiny ones present in other cells of the fly. They are banded with hundreds of rings, some dense, some light, some solid, some mere rows of faint dots. Each chromosome has its characteristic pattern of bands, and each minute section is identifiable (Fig. 3). These patterns persist through generation after generation, so that *even each small segment of every chromosome has its own persistent individuality*.

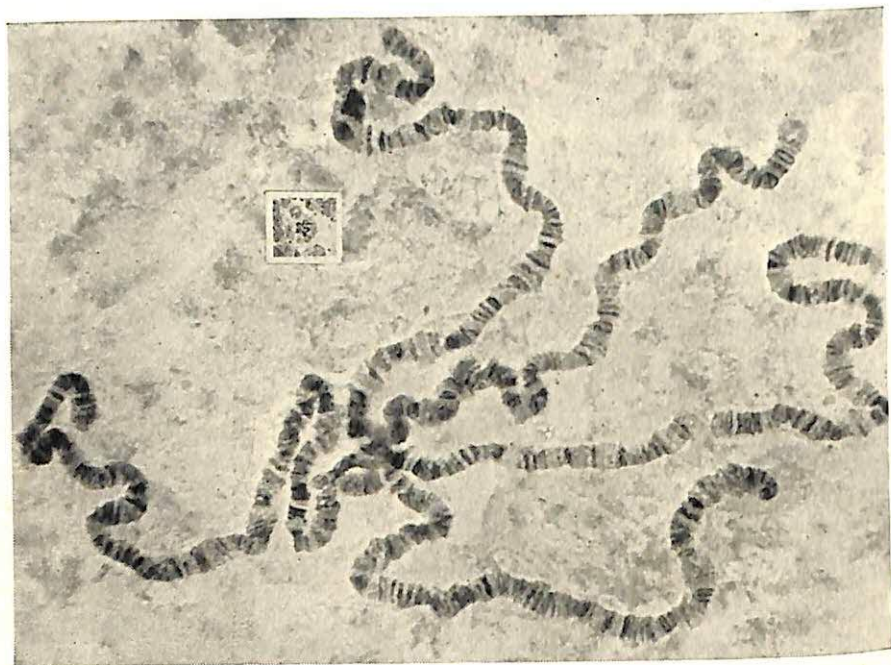


FIG. 3. The giant salivary gland chromosomes of the fruit fly (*Drosophila melanogaster*), magnification about 600 diameters. Inset, the same chromosomes as they appear at the same magnification in most body and germ cells. (Courtesy of B. P. Kaufmann, Carnegie Institution of Washington)

What do all these things show? Even if they fail to demonstrate indubitably that the genes are in the chromosomes, they make it an extremely plausible assumption. The persistent individuality of the chromosomes, even to their minutest segments; the longitudinal cleavage of each chromosome in mitosis, which results in the duplication of each one of these segments; and the accurate distribution to each of the cell offspring of an identical set—these characteristics certainly appear to provide the qualitatively equal division of the genes for which we were looking. The final demonstration of this point rests upon the fact that the behavior of the chromosomes in every case exactly parallels that of the hereditary traits. This can be made clear only when we understand more fully the role of sex in reproduction, which will be treated in Chapter II. However, we may now plausibly assume that the

genes are located in the chromosomes. As we keep this fact in mind, we shall find that the fundamental importance of the nature of cell division becomes increasingly clear.

All mitotic cell divisions are essentially alike

In another book of this series, *The Development of Our Ideas Concerning the Physical World*,¹⁴ Duane Roller says: "Both the permanent aspects and the changes occurring in phenomena must eventually be studied if our picture of nature is to be of most value, but the permanent aspects are usually much the easier to observe and treat. . . . It is a very essential part of the method of these sciences to search for quantities that remain constant amid the variations of nature, for laws that prevail, for concepts that can be retained as permanent. In a less conscious and less systematic way, even our ordinary thinking is permeated with this quest for factors in our environment which we can regard as remaining the same from day to day; for things we can 'count on'; for values we can accept as permanent. Without such self-created reference points for thought and action, existence in this world of incessant and complex change is unthinkable." Here, in the processes of cell division, we may find such a constant biological factor, for the permanency and the stability of life-forms rest squarely upon the duplication and equal distribution of the genes at cell division. The resemblance of offspring to their parents, which we no doubt take as much for granted as we do the assumption that an unsupported object will fall, depends upon the nature of mitosis. Heredity very likely means to us mainly a transmission of variable traits, such as eye color, skin color, resistance to disease, intelligence, and so on. These are of no little immediate importance to us. They may determine our social group, our occupation, our health, our mate; they may even be a matter of life or death to us. But before variation, there must be something to vary from! The essence of heredity lies rather

¹⁴ Unpublished, 1943.

in the statement that all creatures bring forth "after their kind" (Gen. 1:21). This is due to the mechanism of mitosis, which is essentially alike in all living forms. Only from an understanding of this mechanism for maintaining the stability, the *status quo*, of life-forms can we start to investigate hereditary variation.

The process of cell division varies in cells and organisms in an extraordinary number of minor ways, both in the form of the components of the mitotic figures and in their behavior. Nevertheless, this manifold variety can be classified and reduced to a number of types, all linked by transitions. "This circumstance stands as one of the strongest supports of the theory that all mitotic cell divisions are processes essentially like."¹⁵ *And the essential likeness of all forms of mitotic cell division is a most striking witness to the fundamental unity of all living forms.* To understand the situation, therefore, it is necessary only to take one example, and compare it with the other main types.

In white blood cells of the salamander, the nucleus during interphase contains only a few lumps and nodes of dark-staining chromatin and is otherwise clear and homogeneous. In the cytoplasm lies the *centrosome*, a clear gelled area with two minute granules in it (Fig. 4).

The first signs of approaching cell division are seen in the nucleus. In the homogeneous plasm there form long threads, twisted and coiled, and staining deeply with nuclear stains. These are the chromosomes. The nucleus swells somewhat. (At this point the nucleus has entered the *prophase* stage.) As mitosis progresses, the chromosomes become shorter, thicker, and less coiled, and it is then noticeable that each is really composed of two threads, very closely applied to each

¹⁵ This remark by K. Bělař is translated from *Die cytologischen Grundlagen der Vererbung*, p. 32. (Gebrüder Borntraeger, Berlin, 1928.) For those who read German, this is the most complete and best survey yet made of the cytological bases of heredity. The description here given of mitosis in the salamander is paraphrased from it (pp. 28-32). Bělař's death in his early prime, as a result of an automobile accident near Los Angeles, was a severe loss to science.

other. Each chromosome is bent, rather like a hairpin, and the flexures lie close to, or even against, the nuclear membrane. Meanwhile the centrosome has moved to the middle of the cell, and the two granules (known as *centrioles*) have separated a bit as the gel surrounding them liquefies. As they move apart, rays appear radiating from them into the cytoplasm, rays which mingle among themselves to produce a clear area, spindle-shaped. These are the asters and the spindle; and both together are called the *amphiaster*. The spindle area grows larger in every dimension as the centrosomes move farther apart, and is traversed by a myriad of very delicate fibers running from one pole to the other, those on the periphery curved, the central ones straight. The chromosomes are already lying against the face of the nucleus touching the growing spindle. As the nuclear membrane breaks down, they are drawn into an irregular ring, the flexure of each chromosome imbedded in the surface of the spindle. (At this point prophase merges into *metaphase*.)

The ring of chromosomes is next flattened, until the imbedded parts lie approximately in a plane (the equatorial plane) perpendicular to the axis of the spindle. In clear cases, it is possible to see that a mantle of fine fibers (*mantle fibers*) surrounds the *central spindle*, and connects the flexures of the chromosomes with the centrosomes (see also Fig. 5A). The rays of the asters have now reached their maximum size, extending to the periphery of the cell.

For a brief time the chromosomes remain fixed in the ring. Then the halves of each separate and move toward the poles of the spindle, flexures preceding, ends trailing. It is as though they were being pulled apart and toward the poles by the mantle fibers, "inserted" at the flexures. The central spindle lengthens as the chromosomes separate. (This stage is the *anaphase*.)

Short of reaching the centrosomes, the two groups of chromosomes halt. (The mitosis now enters the *telophase* stage.) Within each group the chromosomes press together, until

their limits are made out only with difficulty. The spindle fibers then disappear; the centrioles divide, each aster dimming and then reappearing as they do so. Next a membrane surrounds each group of chromosomes, forming daughter nuclei. These swell in size, and as the chromosomes alter chemically so that they stain less and less, vacuoles appear

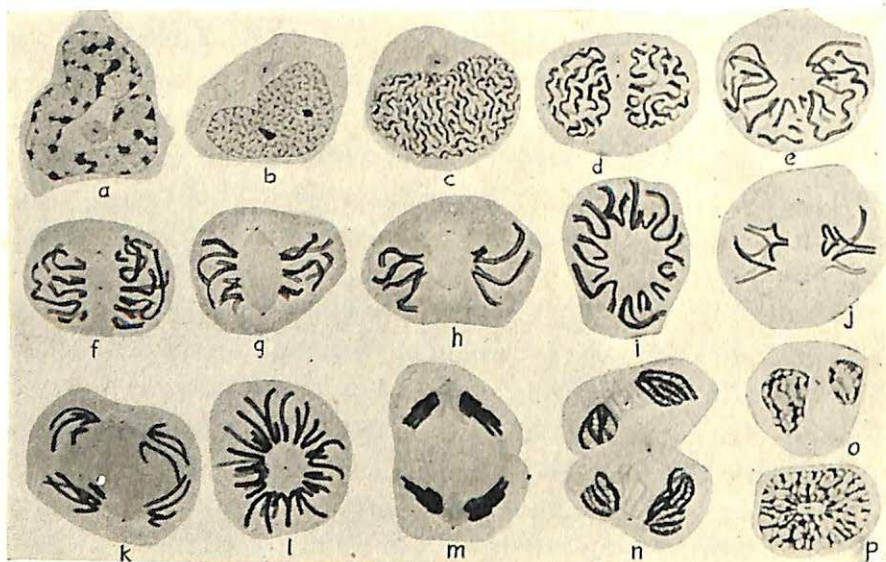


FIG. 4. Cell division in the white blood cells of a salamander (*Salamandra maculosa*). *a-c, e, i, l, and p* are polar views; the remainder are views from the side. *a*, interphase; a convoluted nucleus surrounding a central mass of cytoplasm in which is the centrosome. *b-c*, early prophase. *d*, beginnings of the formation of the central spindle. *e-g*, transition to metaphase. *h-i*, metaphase. *j-l*, anaphase. *m-p*, telophase. (In the polar views of the equatorial and daughter rings not all of the twenty-four chromosomes are visible.) Magnification about 825 diameters. (From Bělař's *Die cytologischen Grundlagen der Vererbung*).

between them. Their outlines grow vague. Projections extend out and form bridges uniting them, until finally, in the typical interphase nuclei, only knots of chromatin betray the former arrangement of the chromosomes (Fig. 4).

In general, the time consumed by mitosis varies considerably with external factors, but thirty minutes to an hour is perhaps average. It is more important to have some idea of

the relative lengths of the stages. These are approximately

Prophase	43%
Metaphase	15%
Anaphase	12%
Telophase	30%

However, the stages have different temperature characteristics; that is, they vary in relative length at different temperatures. They also appear to vary in relative length in different organisms.

More frequently studied is the rate at which mitoses succeed one another, a rate which determines the duration of each cell generation. This is what is generally meant by the terms *mitotic rate* and *rate of cell division*, and they are so used in this chapter (see pp. 38-42).

The two principal variations from the preceding type

In the first of these variants no central (cytoplasmic) spindle is formed by the centrosomes. The true spindle, made of

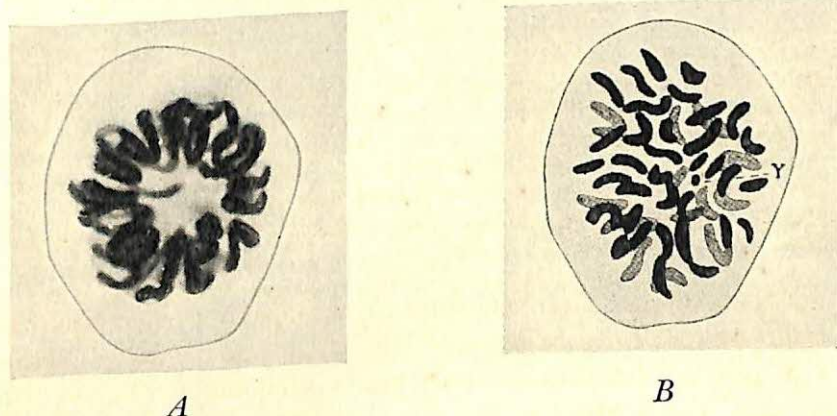


FIG. 5. *A*, chromosomes arranged in a ring around the central spindle. A salamander cell. (Fankhouser. Courtesy of the *Journal of Heredity*) *B*, chromosomes arranged in a plate across the true spindle. A human cell. The smallest chromosome, the one called the Y, is found only in males. (Evans and Swezy. Courtesy of the *Journal of Heredity*)

nuclear material, instead of surrounding the central spindle like a mantle, completely takes its place. The chromosomes, instead of forming a ring, then form a "plate" extending all the way across the equatorial plane of the spindle (Fig. 5B). In the second variant, there is again only a true spindle of nuclear material, but in addition *there are no visible centrosomes or asters*. This latter form of mitosis occurs almost

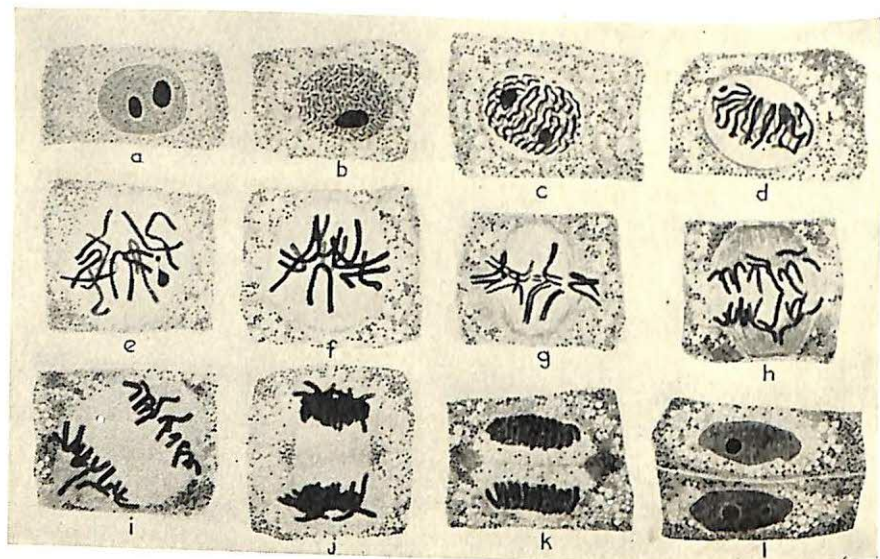


FIG. 6. Cell division in the onion (*Allium cepa*). Observe the characteristic barrel-shaped spindle and the absence of centrosomes and asters. *a*, interphase. *b-c*, prophase. *d-e*, transition to metaphase. *f*, metaphase. *g-i*, anaphase. *j-l*, telophase. Magnification about 825 diameters. (From Bělař's *Die cytologischen Grundlagen der Vererbung*)

universally in the higher plants; it is common in unicellular organisms, and it is characteristic of the two divisions by which the eggs of higher animals become mature (Fig. 6).

In the completion of cell division through division of the cytoplasm there are two principal types. In most animal cells a furrow appears on the cell surface in the equatorial plane of the spindle, during telophase. As the spindle dissolves, the furrow deepens and the cell is pinched in two. In most plant cells, however, granules form an equatorial plate upon

the spindle. They increase in size and coalesce, and the plate grows to the margins of the cell. The deposition of salts, pectin, cellulose, and lignin then commences, until finally the typical double cell wall, each half including two or three distinct layers, is completed. The two major types of cytoplasmic division are linked by a transitional form found in the algae, so that their difference is not radical but merely an accompaniment of the rigid cell wall of cellulose produced by most plants. The essential result is ever the same: the cytoplasm is divided between the daughter cells, and whatever specialized cell structures lie in it, such as plastids in plants, and various sorts of rodlike or minute globular bodies found in animal cells, are separated into two more or less equal groups.¹⁶

CELL DIVISION IS ACTUALLY A COORDINATION OF SEVERAL
SEMI-INDEPENDENT PROCESSES

Thus far we have described cell division as a series of events. Actually, however, it consists of three closely coordinated processes. The changes in the chromosomes are largely independent of spindle formation; and both, in turn, are independent of the division of the cytoplasm. A critical analysis of these will enable us to distinguish the elements that are of fundamental significance. Incidentally, it will furnish a fine example of the complexity of biologic processes, of the numerous interrelations which must be synchronized and coordinated for what might seem at first the attainment of a simple end. Mitosis, as described in textbooks, is frequently oversimplified. We should be on our guard lest we take a very superficial knowledge for real understanding.

In the first place, chromosomes may, on occasion, divide without any division of the other elements of the cell. Now the formation of these daughter chromosomes is merely the

¹⁶ An exception is found in the centrosomes, which, since they lie at the poles of the spindles, are *always* distributed equally.

visible aspect of this first phase of all division; *the reduplication of the genes themselves is the initial step*. At some time between one anaphase and the succeeding prophase—some observers claim even in the preceding prophase—the chromosome becomes visibly double. Has the single string of genes absorbed at each locus¹⁷ the appropriate chemical substances from the nuclear substrate, synthesizing them into the form and pattern of each gene, until the amount of each is sufficient to form two? Or does each gene by a sort of selective crystallization form a twin beside itself? These questions depend largely on the very nature of the gene itself; for if it is composed of a number of molecules, the first method of reduplication will be more probable, while if it is a single molecule, the second is to be preferred. The latter view fits the present scanty experimental data somewhat better.

Without entering the realm of speculation, however, we can draw two important conclusions about gene reproduction. In the first place, the duplication of all the genes takes place simultaneously; the processes are in some way synchronized. This is a significant addition to the original property of autocatalysis we observed in the viruses. Second, the division of the genes, and consequently of the chromosomes, takes place long before any other phase of cell division begins. The chromosomes always seem to be split at least one division ahead of their partition and occasionally, perhaps, even earlier. In anaphase and in the following prophase, when the chromosomes are not too condensed, they are often spirally coiled, and sometimes this coil, called the *chromonema*, can be distinguished from a surrounding matrix. It is this chromonema which is split in preparation for the succeeding mitosis and, no doubt, contains the genes.

Since chromosome duplication so far precedes the other phases of cell division, it is probably valid to regard it as the usual initiator of the next phase. However, synchronization

¹⁷ The term *locus* is used to indicate the position of a gene in the chromosome.

may break down at this point, so that, on the one hand, genes may divide repeatedly without disjoining, and, on the other, spindles may form over and over in the absence of any chromosomes whatsoever. The division of the chromosomes without their distribution may be an abnormal feature of development, as when the spindle mechanism is paralyzed by colchicine,¹⁸ or it may be a perfectly normal one, such as occurs in certain tissues of fruit flies or mosquito larvae. In either case the divided chromosomes remain in a cluster, and the number of chromosomes within the cell is doubled.

The changes in form of the chromosomes during mitosis may be included in this first phase, although seemingly their sole function is to reduce the diffuse chromosomes of the interphase to a compact form capable of disjunction upon a spindle. During prophase the changes consist of (1) an alteration of chemical state, and (2) condensation and contraction. At this stage the one or more *nucleoli*, each associated with special formative regions of particular chromosomes, commence to shrink. As probably their material is distributed to the associated chromosomes, contributing to the matrix which grows up around the invisible gene string, the nucleoli thus disappear while the chromosomes grow thicker and stain progressively darker.¹⁹

¹⁸ The action of colchicine is especially potent and is already of great practical value in plant breeding. Because it stops the course of mitosis in metaphase, the split chromosomes, failing to disjoin, are frequently all re-incorporated in a single nucleus. Thus tetraploid cells arise, which may give rise vegetatively to more vigorous plants with larger or more numerous fruits or doubled flowers. Especially interesting is the possibility of obtaining fertile hybrids. Most hybrids, as is well known, are sterile, but by inducing a doubling of the chromosome number a fertile hybrid carrying two sets of chromosomes from each of the parent species may be procured. One can hardly overestimate the enticing possibilities in the field of hybridization this method holds out. Already new types of cotton and tobacco, as well as a number of fruits, have been produced by its means.

¹⁹ Change in staining capacity indicates a change in chemical nature, since it takes an acid substance to react with the basic (alkaline) dyes which stain chromatin so densely. The acids of the nucleus (nucleic acids) are found nowhere else in nature, except in elementary organisms such as bacteria, where nucleus and cytoplasm are not differentiated.

The chemical alterations and the condensation of the chromosomes are, then, mainly changes of the matrix in which the strings of genes are imbedded. The double coil of the chromonema is simply compressed until its strands are no longer visibly separate. At the end of prophase each chromosome is really double, although its strands are so closely compressed and intertwined as to appear single. In metaphase the splits reappear and the chromosomes then disjoin.

In some cases either whole chromosomes or large portions may remain darkly staining during interphase, or may make their appearance ahead of the other chromosomes as prophase sets in. In *Drosophila* those portions of the set of chromosomes which vanish in the customary way carry practically all the genes, and the visibly persistent regions are genetically barren like the nucleolus. We should therefore distinguish carefully between the chromosomes and the actual strings of genes. The chromosomes contain much nongenic material, which coalesces about the genes during mitosis. Since the nongenic regions carry the points of spindle attachment, we may assume that the dark-staining chromatin is the portion of the chromosome coordinating it with the second phase of mitosis—spindle formation and chromosome disjunction.

The second semi-independent phase of cell division is concerned with the disjunction of the chromosomes and involves the formation of a spindle. That it can be relatively independent of the chromosomal changes is clear from the following facts: (1) When, by chemical or mechanical treatment, all the chromosomes are induced to go to one pole, spindles continue to form in the daughter cell that lacks chromosomes. Their formation keeps step with the mitoses in the adjacent nucleated cells. (2) With needles, a skillful man can extract the entire nucleus from a cell. Spindle formation goes steadily on. (3) A number of chemical compounds (carbon dioxide, quinine, ethyl ether, hydrogen sulfide, potassium cyanide, colchicine) inhibit this phase without seeming to affect gene and chromosome division.

In thinking of spindle formation we should carefully distinguish between the true and the accessory spindles. The true spindle, which brings about the disjunction of the chromosomes, is mainly or wholly nuclear in origin. It is often the sole spindle, but whenever an accessory spindle is present, the true spindle surrounds it, as we have noticed, like a mantle. The fibers of the accessory spindle, which connect the two centrosomes, have been observed indenting the nuclear membrane and leading to its dissolution. Otherwise the accessory spindle seems of little importance. It may even be present or absent in cells of the same organism (axolotl). The evidence cited above concerning the independence of spindle formation from gene and chromosome division applies both to the accessory spindle (1 and 2) and to the true spindle (3).

Why do the chromosomes move toward the poles of the spindle? Genetic evidence is convincing that each chromosome is attached to the spindle by a single structure (its so-called spindle attachment point, or *centromere*). Whenever a chromosome suffers breakage, the resulting fragment that lacks such a structure becomes lost unless reattached; otherwise it will not be drawn onto the spindle nor is it likely to be included in either one of the two daughter nuclei.²⁰ Some force, evident from the relation between the position of the spindle attachment and the shape of the chromosomes, must act upon these points. This does not necessarily imply that the chromosomes are drawn to the poles by the contraction of spindle fibers. Spindle fibers are not typical elastic fibers, for they do not appear to thicken as they become shorter. In the living cell, in fact, no actual spindle fibers can be seen. They are perhaps no more than lines of stress indicating a linear orientation of molecules from pole to pole, such an orientation as is known to occur in fibrous proteins like keratin, the material of our nails and hair. Or perhaps the apparent fibers

²⁰ The chromosomes of bugs (*Hemiptera*) seem to form an exception to this general rule. In some, perhaps in all, species of this order the chromosomes have no single spindle attachment point, and fragments behave like independent chromosomes.

merely indicate that the water in the spindle is unevenly distributed and lies in axial channels between the more rigid portions of the spindle. In at least one organism, a locust (*Stenobothrus*), the movement of the chromosomes is evidently due to a rapid growth of the spindle between the planes where the two sets of chromosomes are imbedded. This growth pushes the chromosomes and the poles farther apart. It is likely that this may be a rather general mechanism, for the distance chromosomes move is frequently proportional to the size of the spindle, which lengthens as the chromosomes disjoin. In *Sciara*, the fungus gnat, a very unusual occurrence takes place. At one division in the formation of male reproductive cells, a half-spindle is formed, with the attachments of all the chromosomes directed toward it. Nevertheless, certain chromosomes move away from the single pole of the spindle along the diverging rays of the half-spindle. Evidences of tension in the chromosomes seem to imply that their spindle attachments are still attracted to the single pole, but that some superior force carries them in the opposite direction. This superior force may reside either in the chromosome itself or in the surrounding island of spindle material which accompanies each chromosome through the cytoplasm.

All in all, the evidence does not lead to any clear or simple interpretation. The most satisfactory explanation is perhaps that, to start with, there is an autonomous repulsion of the chromosomes. This is followed by an expansion of the central spindle material, pushing the two groups of chromosomes farther apart, and a contraction of the two distal portions of the spindle, drawing the chromosomes closer to the poles. Other factors still to be revealed may also play an important part in the disjunction of the chromosomes, that crux of the second phase of cell division.

The third and final phase of cell division is concerned with the distribution of the remainder of the essentials for cell growth and development to the daughter cells. This phase

is also semi-independent. Both chromosomes and nucleus divide commonly enough without any division of the cytoplasm, whenever the activity of the latter is much lowered, as by the inclusion of large amounts of inert food material, or by lack of oxygen, low temperature, a change in the concentration of the surrounding medium, shock, or treatment with such chemicals as lactic and pyruvic acids. On the other hand, cytoplasmic divisions may follow one another in regular succession through the stages of early development in cells entirely lacking nuclei and forming asters but not spindles.

The partition of the cytoplasm, in contrast to that of the genes, is gross and only approximately instead of exactly equal. The more important cell structures clump around the spindle, structures such as the plastids in plant cells, and the rodlike or globular bodies (chondriosomes, mitochondria) found in animal cells and believed to be associated with oxidations. Then, as previously described, in plants a cell plate forms across the spindle and continues to extend until it separates the two daughter cells. These, however, remain attached by their walls of secreted cellulose. In animals and in the maturing reproductive cells in plants, the separation is performed by a constriction of the cell in the equatorial plane of the spindle. The cells, under the control of genetic factors, then either adhere or separate. In the latter event, we observe the characteristic type of cytoplasmic cleavage by which the fission of one-celled animals is accomplished.

THE CELL IN DIVISION SHOULD BE CONSIDERED AS A PHYSICAL SYSTEM

Having now described how the essential structures are apportioned in cell division, we should not forget that, like all life-processes, cell division is dynamic. The cell is the sphere of action of complex interacting forces. Still ignorant as to what these are, we can, nevertheless, learn something of their distribution and nature from the very configuration of the

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cell, both external and internal, and from the changes we have described as taking place.

To begin with, the typical isolated cell is spherical; "that is to say, the uniform surface tension at its boundary is balanced by the outward resistance of uniform forces within." ^{20a} The uniformity of the forces within the cell depends upon the degree of fluidity of the protoplasm. When protoplasmic colloids gel, their fluidity is greatly diminished, and forces at work reach equilibrium more slowly. The spherical shape may thus be distorted. Accordingly, whenever the surface tension fluctuates or varies locally, the cell may pulsate, as a trout's egg does, or protrude in finger-like projections, as do amoeboid cells.

For the same reason the nucleus is also spherical, and because its fluid cytoplasmic surroundings are more constant than the external environment of the cell, it preserves its shape more constantly. Whenever, in the course of differentiation, the consistency of the cytoplasm alters and becomes more solid, the shape of the nucleus becomes correspondingly elongated. There must be, however, some difference in surface tension between the nuclear content and the surrounding cytoplasm. If this "phase difference" were too slight, the nucleus could not cohere on account of the low surface tension,²¹ and would break up into smaller units. Just such scattered nuclear material is found in many rhizopods, and a similar situation leads to the bursting of the contractile vacuoles of fresh-water protozoans. Conversely, nuclear material tends to aggregate within the limit of surface tension, and separate nuclei in a cell may thus often draw together and fuse.

Any interchange of materials between the cell and its en-

^{20a} Thompson, D'Arcy. *On Growth and Form*, p. 164. Cambridge University Press, 1917. This book is the great well-spring of the modern study of growth as related to form. (New edition, 1942.)

²¹ The surface tension between two phases is the difference between their average cohesion, or tendency of like particles to stick together, and the adhesion, or attraction, of the unlike particles of the two phases.

vironment must take place through the surface membrane of the cell, while the living substance to be maintained is substantially its volume. Consequently the relations between the surface area and the volume of a cell are of great importance. Now as a cell grows, its volume ($\frac{4}{3} \pi r^3$) increases far more rapidly than its surface area ($4\pi r^2$). This automatically puts an upper limit to cell size, at a point where the transfer of materials through the membrane is barely adequate to satisfy the needs of the protoplasm. (Of course, cells may apparently transgress such limits through the inclusion of large amounts of inert material, such as stored food.) Long ago it was suggested that, since the cell, upon reaching this size, must either quit growing or divide, the primary impetus to cell division lay here. There is some support for this view. Studies of the ameba have shown that the attainment of a particular cell volume—more specifically of a definite nuclear volume—is, in this animal, a prime factor in initiating mitosis. However, many a cell divides before attaining its maximum size, and in rapidly growing tissues the multiplying cells are nearly always relatively tiny. We may therefore accept the idea that a maximal cell size is imposed by the surface area/volume ratio, without regarding it as more than an accessory factor in initiating cell division.

Of other factors that may be involved in initiating mitosis, we have almost no idea. What underlies autocatalysis, and especially what synchronizes the genes in this activity—these remain major mysteries. Nor do we know how the duplication of the gene strings normally sets going the formation of a spindle.

The centrosomes have often been regarded as autonomous dynamic centers of spindle formation. In animal cells we can see them dividing at anaphase in preparation for the succeeding mitosis, almost as early as the genes themselves. We can also see the asters and the accessory spindle, when it is present, forming around and between the centrosomes as they move apart, while in cells where the centrosomes lie far

from the nucleus to begin with, either they or the nucleus migrate until they reach their usual position. Unquestionably the true spindle is oriented by the centrosomes, and when they are absent it is not pointed but barrel-shaped. Plurality of the centrosomes also throws light on their role. When several sperms manage to penetrate an egg, each of them bringing in a centrosome, multipolar spindles form and the chromosomes are distributed irregularly.

Yet there seems to be no necessity for regarding the centrosomes as possessing genetic continuity like that of the chromosomes. They may arise in nonnucleated fragments of eggs treated with hypertonic solutions,²² or centrifuged, where the original centrosomes have remained in the nucleated portion. It has recently been found that the chromosomes of certain snails can lose their centromeres (spindle attachments), and that these structures then turn into extra centrosomes (or centrioles) that go on dividing in rhythm with the centromeres of the other chromosomes. This discovery makes it apparent that the centrosomes of the spindle and the centromeres of all the chromosomes are similar structures, probably related in origin. It may be that the relationship between them is expressed in the orientation by the centrosomes of the movements of the chromosomes toward the poles.

Whether centrosomes are present or not, the completed true spindle is itself bipolar. The centrosomes, then, must at least represent visibly the dynamic centers at the poles of the spindle. This they orient and give a more pointed shape. The most striking evidence that the centrosome may actually be the dynamic center is that, when it fails to divide, *monasters*—half-spindles—are formed, and the chromosomes, though duplicating normally, fail to separate far (except in *Sciara*, as previously discussed), and consequently become included in a single nucleus. Since divisions with or without

²² In comparing the concentrations of a solution inside and outside a cell, *hypertonic* indicates that the dissolved substance is more concentrated outside than inside.

centrosomes can occur even in the same organism, it seems probable that the difference is mainly between a defined and visible dynamic center of spindle formation in one instance, and a diffuse and indistinguishable one in the other.

We speak of a dynamic center, and certainly the mitotic figure must be a field of some definite sort of force. Few have failed to be struck by its similarity to a bipolar magnetic or electrostatic field. Yet the polarization is really not of this type, as the consistency with which asters *repel* one another shows; when separated they always move farther apart than when they are connected by a spindle.²³ Other types of forces, electrokinetic or osmotic, have been suggested as the mitotic force; but while each theory can be supported by certain facts, there is at present little ground for choosing between them.²⁴

Instead of theorizing on the basis of what may be only superficial resemblances, it might well be more fruitful to see what definite physical changes occur in the cell as it undergoes division. There is, for example, a great increase in the viscosity of the protoplasm. This is clear in comparing the unfertilized eggs of the sea urchin, or similar forms, with just-fertilized eggs in mitosis. The former have little resistance to being stratified by the centrifuge and, when pieces of glass are dropped on them, burst readily. But the eggs in mitosis strongly resist stratification, and if they burst at all under pressure, the viscous contents ooze out slowly. Artificial agents which can stimulate mitosis in unfertilized eggs also cause the cytoplasm to gel. Concentrations of salt either lower or higher than those in the cell can do this and furnish us with a clue. For it is proteins of the globulin type

²³ Opposite magnetic or electrostatic poles form a field like an amphiasier, but *attract* one another.

²⁴ Full treatment of the various theories of mitotic force and the facts bearing on them is to be found in E. B. Wilson, *The Cell in Development and Heredity*, ed. 3, Chap. II, pp. 174-199 (Macmillan, New York, 1925); and in James Gray, *Textbook of Experimental Cytology*, Chap. 8, pp. 155-173 (Macmillan, New York, 1931). A more recent review is that of F. Schrader, "The Present Status of Mitosis," *American Naturalist*, Vol. 74, pp. 25-33, 1940.

which coagulate in this characteristic way; and globulins coagulated by heat or chemicals make realistic amphiasters.

The coagulation of the protoplasm during mitosis is not, however, uniform throughout the cell. The periphery is more solidly gelled, forming a tough ectoplasm; the whole amphiaster is also a gel. Within the more fluid cytoplasm, spindle and asters, carrying the imbedded chromosomes, can be pushed about as a whole by a microdissection needle. The gel is so stable and so elastic that the amphiaster may be greatly distorted, pulled and even twisted into a spiral, without destruction; but too extensive tearing brings about its reversion to the sol state. Ordinarily the mitotic figure tends to orient itself in the greatest dimension of the cell, which is the most stable position for a semisolid suspended in a more fluid medium.

Cleavage by deepening furrows and constriction is almost always associated with the type of mitosis in which there are definite centrosomes and asters at the poles of the spindles. Changes in viscosity play a part here as in spindle formation, so it is not surprising to find that carbon dioxide, which alters the hydrogen ion concentration, and so affects sol-gel reversibility, has a profound effect on both spindle formation and cleavage; or that high osmotic concentrations dissolve both spindle and asters irreversibly, thus checking both chromosome disjunction and cytoplasmic division; or that other chemicals have an effect upon both, which is reversible when not too severe.

While the major part of each aster is firmly gelled, the centrosomes are clear and fluid. The thin tapering rays of the asters are also fluid, and along them the plasma flows in toward the centrosomes, where it accumulates. This can be readily detected, for the centrosome steadily increases in size, and solid particles or oil droplets introduced into the rays migrate toward it. The bulk of each aster consists of the cytoplasm between the rays. This is most strongly coagulated next to the centrosome, and peripherally grows progressively

more fluid. The growth of the asters depends upon the area over which they can extend—this can be shown by cutting an egg into fragments when the asters are still small—and the position and depth of the cleavage-furrow in turn vary with the size of the asters.

Yet after all, asters are not absolutely necessary to constriction. This is especially clear in isolated cells, such as white blood cells or certain kinds of cells growing in tissue-culture, which have no asters but which, nevertheless, divide by constriction. First, they become ellipsoidal. Then, as the equatorial constriction appears, blisters are extruded and resorbed at the poles, and currents-flow superficially from the poles to the equator, where they turn inward and flow back to the poles. These blisters and currents are just what would be set up by a lowering of surface tension at the point closest to each pole, or by an increase of surface tension along the equator. The change in surface tension may be due to the approach of the reconstructed nuclei to the surface of the cell. The completion of fission appears, from studies of amebas and tissue-culture cells, to be essentially locomotory. The two halves simply crawl in opposite directions until they part company! In the absence of asters, constriction is therefore probably due to a change in the surface tension of the cell, followed by locomotion.

In cells with asters the outer layer is clear and tough, and much less fluid than the underlying cytoplasm. It collects at the equator, and, according to at least one series of observations, actually *grows* in toward the center of the spindle. Hence it serves much as do the cell plate and cell wall of plant cells, holding the two daughter cells together, although without their rigidity. Without doubt, therefore, the asters are connected with the mechanics of cytoplasmic division in cells which remain associated.²⁵

²⁵ The chapter by Robert Chambers in the *General Cytology* edited by E. V. Cowdry (University of Chicago Press, 1924) deals with the microdissection analysis of the physical structure of the cell, during mitosis as well as in the interphase. It is somewhat out of date and needs to be supplemented.

CELL DIVISION IS SIGNIFICANTLY AFFECTED BY
CHEMICAL SUBSTANCES

The role of chemical substances in stimulating cell division has been indicated in a number of observations. Mitosis in tissue cells is speeded up by foreign blood serum; in white blood cells by bacilli. Malignant tumor cells produce a substance stimulating the mitotic activity of tumor tissues, and substances found in the vascular bundles of plants promote cell division in the healing of plant wounds. A cluster of cells of common origin has a marked tendency to divide synchronously. The general tendency of undifferentiated cells to divide rapidly, but to slow down and acquire different rates of division as they age and specialize, also indicates the presence of chemical factors which control the occurrence of mitosis.

Certain substances have been found which markedly affect growth in plants, either by stimulation or by inhibition. Three of these growth hormones, or *auxins*, as they are called, are known at present, namely, auxin *a*, auxin *b*, and heteroauxin. They are complex organic acids. Though they affect growth chiefly by cell enlargement (see Chapter IV, p. 197), auxin *a* and heteroauxin also stimulate cell division, both in primary and in secondary growth.²⁶ However, to do this requires concentrations some ten thousand times greater than those to stimulate cell enlargement, and such concentrations almost certainly do not occur normally in cells. We may therefore well regard the effects of auxin and hetero-

Gray (*op. cit.*) is excellent, though biased slightly by his own views of the mechanism of cytoplasmic cleavage. Chapter IX and the first part of Chap. X (to p. 150) of T. H. Morgan, *Experimental Embryology* (Columbia University Press, 1927) are also good. More recent are L. V. Heilbrunn, *An Outline of General Physiology*, Chaps. VIII and XLII (W. B. Saunders, Philadelphia, 1937), and W. Seifriz, *Protoplasm* (McGraw-Hill, New York, 1936).

²⁶ Primary growth in a plant is that which takes place at growing tips (meristem) in young tissues, such as embryonic root and plumule, root tips, and buds of all kinds. Secondary growth is that which increases the diameter of roots and stems through the activity of the cambium layer.

auxin on cell division as a sort of indirect chemical stimulation. Since the processes comprising cell division and those prerequisite to it are extremely complex, and the substances involved are legion, it is not surprising that many substances can be found, especially those affecting general metabolism and oxidative rates, which also influence mitosis. Among these, besides the auxins, are other hormones such as adrenalin and insulin, organic acids such as acetic and citric acids, salts such as sodium chloride, and sugars such as levulose.

Among the elements known to be essential to life is sulfur. In the cell this element is combined chiefly with hydrogen, forming what is called the *sulfhydryl group* ($-SH$) attached to some organic combination. Chief sulfur-supplying constituent of an adequate diet is the amino acid, cystine. In cystine two sulfur atoms are linked to each other and to organic groupings, so that, if we symbolize the latter in general by R , cystine can be represented as $R-S-S-R$. Cystine is easily reduced to two molecules of cysteine, which is accordingly $R-SH$. Either cysteine or cystine combines with two other amino acids to form glutathione, which therefore exists in two states $R-SH$ and $R-S-S-R$ (see Note D, p. 52). Now glutathione ($R-SH$) is present in most, if not all, living cells. It is one of the basic chemical substances upon which life depends; and the characteristics of life must to some degree depend upon its chemical properties. Its distribution in rapidly growing tissues, such as the root tip of an onion or a regenerating segment of the hydroid animal *Obelia*, corresponds to the intensity of metabolic activities (oxygen consumption, carbon dioxide production, reducing power of tissues, cellular electric potentials).²⁷ It is therefore highly

²⁷ *Metabolism* is customarily defined as the sum of all chemical and physical changes taking place in an organism, yet it is generally used in a much more restricted sense, for the definition just given is virtually synonymous with *life* and is so inclusive as to be well-nigh meaningless. However, all of these activities either release energy or require it; and since nearly all synthetic activities, with the exception of the photosynthesis carried on by green plants, get their energy from the oxidations which are the energy-releasing processes in nearly all organisms, the intracellular oxidations may be taken

significant that glutathione, in either form, and perhaps other organic compounds of the R-SH type, too, stimulate mitosis in plant and animal cells.

The importance of sulfhydryl in controlling mitosis is shown by the following instances: (1) In the absence of sulfur in the environment, the rate of fission of a protozoan (*Chilomonas*) diminishes rapidly until death occurs. This slowing up of the rate of division seems due to the rapid decrease in internal sulfur per cell, as fission proceeds and the existing store is thereby steadily halved. The stimulating effect of the sulfhydryl upon mitosis is greatest at a certain optimum concentration, both above and below which it lessens. (2) In the ameba, cell volume (and especially nuclear volume) is, as we have noticed, a prime factor in controlling the rate of mitosis. Glutathione causes the nucleus to attain the optimum size for mitosis more rapidly. Thus nuclear division is stimulated, although cytoplasmic division does not always follow. (3) Copper and lead inhibit nuclear growth and division, presumably by reacting with sulfur and breaking up the -SH group. (4) The rate of cell division is positively correlated with potential size in rabbits, and potential racial

as a measure of the entire metabolism. This has naturally led to a narrower usage of *metabolism*, in the sense of the oxidations going on in an organism and their more immediate consequences.

The total rate of oxidation in an organism or tissue can be measured by the amount of oxygen it consumes. Measurement by the amount of carbon dioxide produced involves an assumption that all oxidations are carried to completion, but as a rule the method may not be seriously in error. Measurement of the amount of water produced is inaccurate because of the small likelihood that all of it will be eliminated, at any rate promptly. (The same objection would naturally apply to the measurement of carbon-dioxide production in a green plant, in the presence of light.) For every oxidation there must be a complementary reduction, so that measurement of the reducing power of a tissue is equivalent to measuring its oxidative capacity. Finally, the rate of oxidation may be estimated from the amount of some form of energy produced. Heat is always released, and a considerable proportion of the total energy is thus lost, but comparative heat production is very likely a better measure of the efficiency of different tissues or organisms than of their relative total oxidations. Electric energy also appears to be universally produced in cells, but opinion today is still sharply divided as to whether it is directly related to cellular oxidation or not.

size is similarly correlated with the glutathione content of the newborn rabbit. (5) The hairlessness of hairless rats is due to a gene that also renders its carriers unable to produce cysteine ($R-SH$) from cystine ($R-S-S-R$). The hairlessness is very likely a secondary result of the chemical defect, being produced by way of the influence of the latter over cell division. Thus the last two instances indicate that certain genes control cell division through this chemical mechanism.

Although we can detect no change in heat production either as interphase gives way to mitosis or during the progress of mitosis, there is a clear-cut fluctuation in oxygen consumption, which has been correlated with changes in the concentration of the $R-SH$ glutathione. This must mean that the interphase and the several phases of mitosis really differ in metabolic state. A further sign is that mitosis, like all metabolic processes, is retarded by cold, and the temperature coefficients,²⁸ which are of the order of those of chemical processes, vary from stage to stage (highest in prophase; lowest in anaphase).

But although the oxygen consumption changes during mitosis, this does not prove that cell oxidations control mitosis. As a matter of fact, many substances which affect respiration—carbon monoxide, for example—do not affect cell division at all. On the other hand, the events of cell division seem to influence the rate of oxidations rather than the reverse. Whether, then, the effect of glutathione upon cell division is independent of its role as an oxidative enzyme, or whether, as is more likely, the two roles are in some manner interrelated, and, if so, how—the answer will certainly be of major importance to our understanding of life.²⁹

²⁸ The temperature coefficient of any process is the number of times the rate of the process increases for each rise of 10° C.

²⁹ On the sulphydryl problem, only original papers are available. The rather contrary views of Hammett and of Mast and Pace should be compared critically. The former has written a great deal, but the essence of his ideas can be obtained in the one paper listed here. His views have been severely criticized by a number of workers.

See Hammett, F. S. "The Natural Chemical Equilibrium Regulative of

After careful observation, the similarities and dissimilarities of the mitotic cycle in hundreds of forms have today been summed up, and any possibility that purely descriptive morphology can throw further light on its nature is largely exhausted. For a deeper understanding of the intricate nature of cell division, we must turn to biophysics and biochemistry. Already a beginning—very tentative and uncertain, to be sure, but still a beginning—has been made.

REPRODUCTION AT ITS SIMPLEST IS CELL DIVISION

For the thousands of varieties of plants and animals which live as single cells, the process of mitosis and cytoplasmic division, followed by separation of the two newly formed cells, is reproduction. The *Paramecium* and the ameba, the diatom and the desmid through this fission multiply at astounding rates. This throws a great deal of light on such basic life phenomena as sex, variation, and natural death! Sex, which we have perhaps considered almost a synonym for reproduction, is here divorced from it entirely. Even in protozoa, where a sexual process (conjugation) does occur, it seems to be quite unnecessary, for in one laboratory some 20,000 generations of *Paramecia* have been raised without it, by fission alone. In the evolution of life, sex must be a relative newcomer in comparison with reproduction. While it is true that we can see no mitosis in the smallest of all living forms, the bacteria, we do see fission there; and the elaborate mechanisms of mitosis for the distribution of genes, protoplasm, and foodstuffs may well be unnecessary in so simple a form. Even here, however, we must suppose that the ability of certain protein molecules to duplicate themselves is present. Given a suitable substrate, such as protoplasm, each such molecule can become two where it was but one!

Growth by Increase in Cell Number," *Protoplasma*, Vol. 11, pp. 382-411. 1930.
Mast, S. O. and Pace, D. M. "Relation between Sulfur in Various Chemical Forms and the Rate of Growth in the Colorless Flagellate, *Chilomonas Paramecium*," *Protoplasma*, Vol. 23, pp. 297-325. 1935.

This is like the protein molecule of the virus, which can also duplicate itself under appropriate conditions, although otherwise it cannot. *This duplication is, then, the very essence of reproduction, coeval with, perhaps even preceding, the origin of life itself.*

What is the extent of individual variation under these circumstances? Clearly enough, since each chromosome is split and each gene duplicated, and since each cell receives a complete set, the sets of genes carried by offspring produced by fission must be identical. If we begin by isolating a single organism, the continuation of this process of cell division will soon result in a whole race of individuals carrying identical genes. Such a race is called a *clone*. Whatever variation occurs in a clone, provided the genes remain stable, must result solely from differences in the environment to which the individuals are exposed; and, were they to live together within a completely uniform environment, both they and their descendants would manifest no variety whatever. They would form a race of individuals much more alike than two identical twins among mankind. Attempts have been made to split up such clones into races which would perpetuate through heredity the variations resulting from the environment, but they have all been unsuccessful. For example, H. S. Jennings, of Johns Hopkins University, by selecting large and small *Paramecia* in a pure race, tried to establish different stocks which would maintain these differences, but to no avail. Large and small alike had progeny of the same average size. The same was true for reproductive rate and for resistance to heat or chemicals. Other men have had no better fortune in trying selection within pure lines of bacteria or yeasts.

In plants which will grow from cuttings of stems, roots, or other vegetative parts, and in such animals as reproduce by budding or fission, or in which females produce daughters from unfertilized eggs, descendants carry sets of genes identical with those present in their ancestors, and pure lines may

be propagated. Here again, selection within the pure line fails to establish races hereditarily different. This has been tried in *Hydra*, plant lice, the lower crustacea, and in many other forms. So well recognized is the principle in plant breeding that florists and horticulturists have long made a general practice of propagating their valued strains vegetatively.

In the higher animals, pure lines cannot exist, but fission may occur during the development of a fertilized egg. Either at the two-celled stage or later, an embryo may divide into two or more separate parts, each of which becomes an individual. This phenomenon will be considered in other aspects later, but here we may note the practical identity of such individuals—not with either of their parents, to be sure, but with one another—whether armadillo quadruplets or Dionne quintuplets.

And what of death? Is there among the one-celled organisms no ageing, no wearing out of the protoplasm or of the genes? The answer seems to be that cells removed from an organism can grow, divide, and grow again in a ceaseless cycle as long as external conditions are suitable. The cells may even attain a certain degree of differentiation, and cling together in a loosely organized, simple tissue. The famous cells from a chicken's heart have been living and growing in this way for thirty years since the culture was originally started by Alexis Carrel. Their protoplasm does not die; it is simply divided among the daughter cells.

Protoplasm does not die because as it wears out it is renewed. There is a constant exchange of materials between environment and cytoplasm. Foods, including oxygen, enter the cell; wastes, including carbon dioxide, leave it. Yet this metabolic activity of itself seems no more to produce ageing and death than the vortical whirling of water, in a basin into which it is running steadily from a tap and from which it is carried off equally steadily by the drain, results in exhaustion and end. Senescence and mortality in the cell appear rather to depend on three things. The primary cause appears to be

specialization. In the higher organisms this takes the form of an aggregation of "specialist" cells. The aggregation is naturally attended by an increasing difficulty in maintaining for all cells a regular supply of foodstuffs and a regular removal of wastes. Thus the cell is gradually choked by its own products and is slowly starved. We pay the price of death for the division of labor in our bodies. Our complexity is our doom.³⁰

As the division of labor among a group of cells increases, the reproductive function itself is restricted to fewer and fewer of their total number. This is well illustrated in the members of the Volvox order, simple types at the bottom of the plant kingdom. *Chlorogonium* (Fig. 7A) is at first a single cell, bearing at one end two whiplike lashes (flagella) with which it swims, and containing a number of chloroplasts enabling it to carry on photosynthesis. By cell division, this individual becomes two cells; then the two, four. However, as a capsule is secreted around the first individual, the four are not entirely independent, but are confined for a time (Fig. 7B). Eventually the capsule bursts, and each of the four is set free to repeat the cycle. Here, evidently, the capacity to reproduce is not limited. Each of the four is reproductive, and, if we think of the group as the individual, each cell is a *spore*, or reproductive cell. *Pleodorina* is like *Chlorogonium*, except that the process of cell division within the secreted capsule continues until there are 32-128 cells in all (Fig. 7C, D). These are all much alike, resembling the *Chlorogonium* individual, except that those at one end of the colony are smaller than the others. When the capsule ruptures, all but these small cells can form new colonies by cell division; but the small cells, solely vegetative, perish! *Volvox* is much larger yet, with more than a thousand cells arranged over the surface of a great spherical capsule (Fig. 7E).

³⁰ The first two chapters in H. S. Jennings' book *Life and Death, Heredity and Evolution in Unicellular Organisms* (Richard G. Badger, Boston, 1920) deal with these questions, and are extremely thought-provoking.

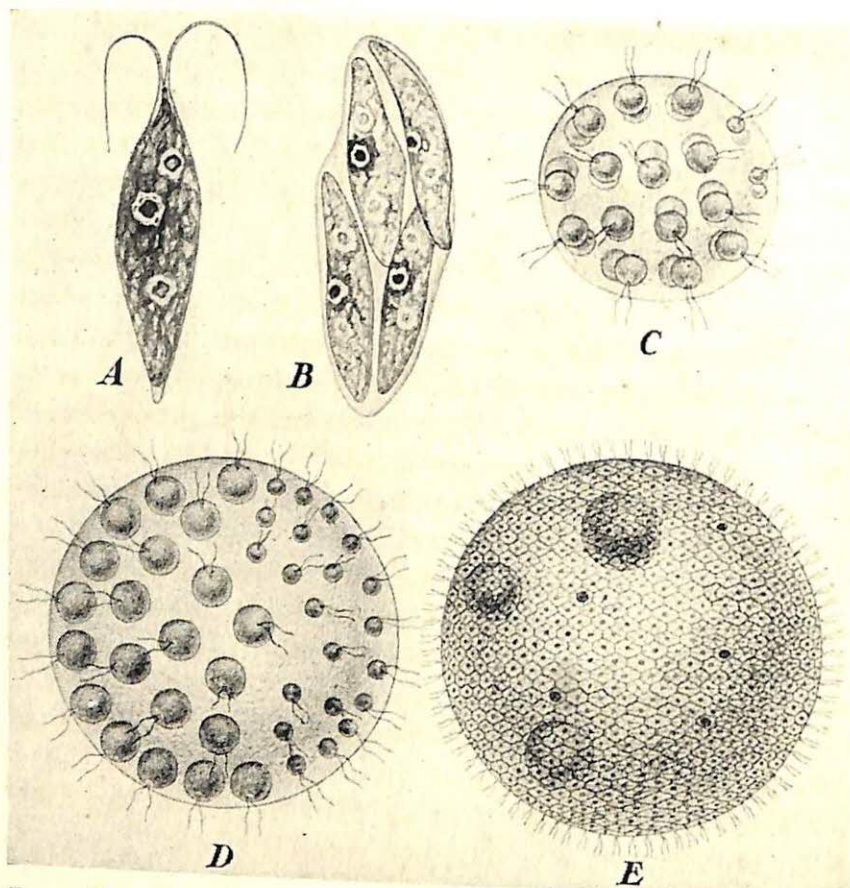


FIG. 7. The simplest division of labor among cells, that of the vegetative and reproductive functions, as seen among green flagellates of the Volvox order, not drawn to scale. *A*, *Chlorogonium*, a solitary individual. *B*, *Chlorogonium*, a group of four, undifferentiated. *C*, the colonial form *Pleodorina illinoensis*, with four small solely vegetative anterior cells and twenty-eight large reproductive posterior cells. *D*, *Pleodorina californica*, with relatively more vegetative cells and fewer reproductive cells. *E*, *Volvox*. Each cell is located in a hexagonal zone of the gelatinous sphere, and communicates with its neighbors by fine strands of protoplasm. There are relatively few of the colonies are developing within the mother sphere. (*A* and *B* redrawn from Hartmann; *C*, *D*, and *E*, redrawn from Plunkett's *Elements of Biology*. Courtesy of Henry Holt and Company)

The reproductive function is here limited to about a third of the cells in one half of the colony. These can drop down into the center of the hollow ball, and form daughter colonies, small spheres within the larger one.³¹ Eventually they are set free when the parent colony, grown old, ruptures and dies.

The power to form reproductive cells (whether spores or sexual gametes) is still further limited in the higher plants and animals, where it is confined to definite reproductive organs. With the advent of cell aggregation and differentiation there is a progressive decrease in the proportion of cells that retain the capacity to produce a new individual when isolated from the organism. Cells which specialize upon other functions lose this power.

The isolated cell or one-celled plant or animal possesses all the general capacities of the specialized cells of an organism such as man, who is billions of times greater and indescribably more complex; but its capacities are not developed to the fullest. The protoplasm flows around food material, digestive enzymes are secreted, the liquefied food matter is absorbed and transported to all parts of the cell by diffusion and by currents. Oxygen enters the cell, the foods are oxidized to yield up their energy, or are synthesized to become constituents of the protoplasm; wastes are formed and excreted through the cell membrane. The released energy appears in various forms—heat, light, electricity, chemical energy, mechanical work. These are controlled and coordinated, so that behavior is related to environmental stimuli. The course of differentiation consists of progressive specialization by certain cells upon some one of these activities. The processes of differentiation are controlled by the genes; and the nature of the genic pattern responsible for the multifarious variety of life will be considered more fully in Chapter II.

³¹ Sexual reproductive cells (*gametes*) are also produced.

NOTE A. ILLUSTRATIONS OF THE BELIEF IN SPONTANEOUS
GENERATION BY TWO ANCIENTS AND TWO MEN OF THE
MIDDLE AGES

- Lucretius: "Even now there come out of the ground animals
(99-55 B.C.) which are brought forth by the rain or the warm exhalations of the sun." (*De Rerum Natura*)
- Vergil: "Kill an ox two years of age, whose young horns are just beginning to curl upon his brow, place him in a narrow enclosure strewn with leaves of thyme and rosemary freshly gathered, and soon from this fermenting humor there rises a swarm, which fills the air like rain from summer clouds."
- Paracelsus: "Let the sperm of a man by itself be putrefied
(1490-1541) in a gourd glass, sealed up, with the highest degree of putrefaction in horse-dung, for the space of forty days, or so long until it begins to be alive, move, and stir, which may easily be seen. After this time it will be something like a man, yet transparent, and without a body. Now after this, if it be every day warily, and prudently nourished and fed with the arcanum of man's blood, and be for the space of forty weeks kept in a constant, equal heat of horse-dung, it will become a true, and living infant, having all the members of an infant, which is born of a woman, but it will be far less. This we call *Homunculus* or artificial man. . . . Now this is one of the greatest secrets, that God ever made known to mortal, sinful man." Comments Cole: "Paracelsus disliked woman, which may explain his attempt to produce a foetus without the cooperation of a mother."
- Van Helmont: A recipe for procuring rats. . . . "All that is required is to cork up a pot containing corn with a dirty shirt; after about twenty-one days a ferment coming from the dirty shirt combines with the effluvium from the wheat, the grains of which

are turned into rats, not minute or puny, but vigorous and full of activity." ³²

NOTE B. THE RELATION OF BELIEF IN SPONTANEOUS GENERATION TO THE CONFLICTING DEVELOPMENTAL THEORIES OF PREFORMATION AND EPIGENESIS

Swammerdam, in the seventeenth century, seems to have been the first to deny the spontaneous generation of life. Redi, a Florentine physician of the same period, had demonstrated conclusively that maggots appear in decaying meat only when flies have access to it. Harvey, his British contemporary, who discovered the circulation of the blood, was able through keen observation of the developing embryos of mammals, birds, and lower types, to conclude rather sententiously: "All animals, even those that produce their young alive, including man himself, are evolved out of the egg." Yet neither Redi nor Harvey could quite free himself of the belief that such tiny creatures as internal parasites and various sorts of insects arise *de novo*. Harvey, studying the development of the chick within the egg, concluded, like Aristotle, that organs arise successively by differentiation from the unspecialized substances of the egg.

Swammerdam, on the contrary, greatly influenced against this epigenetic view by his investigations of the development of insects, saw in them a gradual unfolding of pre-existing parts. Spermatozoa had only recently been discovered, and the famed Dutch microscopist, Leeuwenhoek, believed that life itself came from the male through the spermatozoon, while the egg furnished only nourishment and capacity to develop. Swammerdam's preformation theory, in spite of subsequent distortion by factions contending for supremacy of egg or sperm, was the first attempt to subject ontogeny to natural law, to explain development in mechanical terms.

For the next two hundred years, however, the question of the existence of a spontaneous generation of organisms was closely tied to the controversy between the preformationists and the epigenesists. The latter began to prevail following the insistence by Wolff (1759) that the earliest phases of development can actually be seen microscopically and are totally inconsistent with any

³² Cole, F. J. *Early Theories of Sexual Generation*. Oxford University Press, 1930. Here is a book full of interest to those who take zest in tracing the growth of our modern conceptions. The preformationist-epigenesis controversy is well covered.

theory of preformation. With the discovery of the mammalian egg and the mode of its growth within the ovary by von Baer in 1828, epigenesis was generally accepted. The discredit of the preformationist ideas was accompanied by a resurgence in the belief in abiogenesis (spontaneous generation). As microscopes improved, the myriads of bacteria, microscopic plants and animals present in the waters became evident in almost innumerable variety. Their life cycles were too difficult to trace with the methods and equipment of the time, and they had a way of inevitably turning up in any situation where there was a food supply. Many, indeed, believed that the origin of these in vessels which had been free of them was actually proved. These things explain the scorn and vehemence met by Pasteur when, in 1860, he put forward the claim that he had demonstrated that even these minute forms arise from organisms already present.

NOTE C. PASTEUR ON SPONTANEOUS GENERATION

In his lecture before the Sorbonne, on April 7, 1864, Pasteur summed up his crucial experiment in these words: "Here, gentlemen, is an infusion of organic matter of perfect limpidity, limpid as distilled water, and extremely alterable. It has been prepared today. Even tomorrow it will contain animalculae, little infusorians or flocculi of molds.

"I place a portion of this infusion of organic matter in a flask with a long neck, like this one. Suppose I boil the liquid and then let it cool. At the end of some days, molds or infusorian animalculae will have developed in the liquid. By boiling, I have destroyed any germs which might exist in the liquid and on the surface of the wall of the flask. But as that infusion comes again into contact with the air, it becomes altered, as do all infusions.

"Now suppose that I repeat this experiment, but that, before boiling the liquid, I draw out (with an enameled lamp) the neck of the flask into a point, leaving, however, the tip open. This done, I bring the liquid in the flask to a boil, then I let it cool. Now, the liquid of this second flask will remain completely unaltered, not two days, not three, four, not a month, a year, but three or four years, for the experiment I am telling you about is already that long. The liquid remains perfectly limpid, as limpid as distilled water. What difference is there then between those two flasks? They contain the same liquid, they both contain air,

both are open. Why then does this one become altered, while that one does not? Here, gentlemen, is the only difference between the two flasks: In this, the grains of dust which are suspended in the air and their germs can fall through the neck of the flask and come in contact with the liquid, where they find appropriate aliment and develop. Thence, microscopic beings. In that, on the contrary, it is not possible, or at least it is extremely difficult, unless the air is violently agitated, for the dust motes in suspension in the air to enter into the flask. Where do they go? They fall on its curved neck. When the air flows back into the flask, on account of the laws of diffusion and the variations of temperature, the latter never being abrupt, the air enters slowly, sufficiently slowly for the dust and all the solid particles that it carries to fall at the opening of the neck, or to stop in the first part of the bend.

"This experiment, gentlemen, is full of instruction. For notice well, that everything in the air, everything save the dust, can very readily enter the interior of the flask and make contact with the liquid. Imagine whatever you choose in the air, electricity, magnetism, ozone, even things of which we are still ignorant, all can enter and come in contact with the infusion. There is only one thing which cannot enter easily, the dust suspended in the air, and the proof of that is, that if I shake the flask vigorously two or three times, in two or three days it will contain animalcules and molds. Why? Because the return of the air has taken place violently and has carried dust in with it.

"And consequently, gentlemen, I too could say, showing you this liquid: I have taken my drop of water from the immensity of creation, and I have taken it full of nutrient jelly, that is, speaking scientifically, full of the elements appropriate for the development of inferior beings. And I wait, and I watch, and I question it, and I demand that it be willing to recommence for me the act of primitive creation; how beautiful a spectacle that would be! But it is mute, mute since these experiments were begun several years ago. Ah! that is because I have kept from it, still keep from it at this moment, the only thing it has not been given to man to produce, I have kept from it the germs which float in the air, I have kept from it life, for life is the germ, and the germ is life. Never will the doctrine of spontaneous generation recover from the mortal blow which this simple experiment has given it."

Pasteur then went on to recount how flasks containing infu-

CHAPTER II

The Origin of Differences in Hereditary Patterns

WE HAVE seen in Chapter I that mitosis brings about an exactly equal distribution of the genes, and that reproduction based solely upon mitotic cell division must result in genetic identity, accordingly limiting variation to the effects of the environment. Yet variety, well-nigh universal among life-forms, is undoubtedly to a great extent genetic, as the differences between families show. Reproduction among most organisms must then involve more than mere isolation of a reproductive cell formed through cell division. As we know, it does, usually being associated with sex.

AMONG THE HIGHER PLANTS AND ANIMALS, INDIVIDUALS USUALLY
ARISE BY THE FUSION OF TWO REPRODUCTIVE CELLS

Sex is fundamentally the capacity to form certain sorts of reproductive cells, known as *gametes*. The essential feature of these cells is that they fuse to give rise to a new individual, thus differing from spores, which can begin development autonomously. The fusion of gametes is usually called *fertilization*, a word connoting an impetus to growth. The fusion has two consequences. One result, indicated by the word itself, is the removal of the block which normally prevents a gamete from resuming cell division. (We shall consider this aspect further in Chapter III.) The other is of great importance in bringing about hereditary variation: it is the

aggregation within a single cell, and hence in the individual developing from that cell, of genes derived from different parents. Since the impetus to growth and development can be provided by other means, we shall use the term *syngamy* for the fusion of gametes, in order to emphasize its hereditary consequences. The single cell, formed by the combination of gametes from different parents, is called a *zygote*, from the Greek word for yoke.

In simple organisms gametes are alike and are often indistinguishable from other cells. However, among most organisms there is a division of labor between the two gametes. One takes over the function of supplying the zygote with the necessary protoplasm, food, and cell structures. It attains

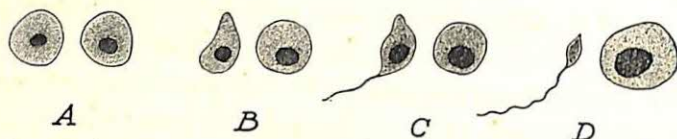


FIG. 8. Progressive steps in the division of labor between male and female gametes, as seen in various gregarines (parasitic protozoans). A, gametes alike. B, gametes slightly different. C, gametes considerably different. D, gametes typically differentiated.

a larger and larger size, consequently becoming less mobile, and is known as the *megagamete*, or *ovum*. This is the female gamete. The other becomes especially fitted for locomotion, and proportionally smaller and smaller. It is the male gamete, and is known as a *microgamete*, or *sperm* (spermatozoon). The differences between ovum and sperm have, no doubt, arisen in successive evolutionary steps. At least, a progressive series of such steps can be arranged from the types of gametes to be found in a number of groups of the simpler plants and animals, as, for example, among certain unicellular parasites (gregarines), which live in the body cavities of vertebrates (Fig. 8).

In man, the gametes differ quite characteristically. If we look at the sperm, we find that it has a small oval head, flat-

tened at the tip. The head of the sperm is formed from the highly condensed chromosomes of the nucleus with a little cap of granules from the cytoplasm. A short neck and a slender middle-piece come from the centrosome. A long delicate whiplike tail propels the sperm. This is produced by the elongation of the cytoplasm around a central filament, which grows out of one of the two centrioles, those minute granules at the core of the centrosome. So very tiny is the whole sperm that, according to calculation, all the sperms which will take part in the production of the next generation of mankind, some two billions of them, could be packed into a space half the volume of an aspirin tablet. (See Figs. 9B and 10A.)

The sperms of other animals are very similar, and the same parts can be identified in each (Fig. 10). In many instances the anterior cap is curiously modified, pointed, coiled, even hatchet- or corkscrew-shaped.¹ Among crabs and other crustacea peculiar sperms are formed with a central body surrounded by radiating arms. Here the central region is the compact nucleus, the radiating arms are outgrowths of the neck, and a cylindrical or conical part opposite the nucleus is homologous to the tail. The sperms of certain flatworms have two flagella instead of a single tail-filament.

Plant sperms are also essentially similar. The motile types found in the lower plants usually have two whiplike flagella, like those of the flatworms just mentioned. Or they may have four or more, a step toward the situation in the ferns. Here the nucleus is coiled about the rounded cytoplasm, and the coil is continued by a structure from which delicate hairlike cilia stand out in tufts. This structure arises from a cytoplasmic body similar to that which forms the anterior cap of the head of animal sperms. The free-swimming sperms of the ferns and their allies are connected by transitional types with the nonmotile microgametes typical of seed plants. The ginkgo tree and the cycads, for instance, have simplified

¹ Beware of jumping at conclusions! These are probably not modifications for *violently* penetrating the egg.

*B**A*

FIG. 9. *A*, the human egg. A two-day-old unfertilized human ovum, photographed by Dr. Gregory G. Pincus. Magnification about 500 diameters, or millions of times by volume. The black spot at upper center is the region of the nucleus. *B*, human sperms. Photographed from a slide prepared by Dr. Seymour F. Wilhelm. Magnification about the same as egg in *A*, showing relative size of a single sperm compared with the human egg. (From Scheinfeld's *You and Heredity*. Courtesy of Frederick A. Stokes Company)

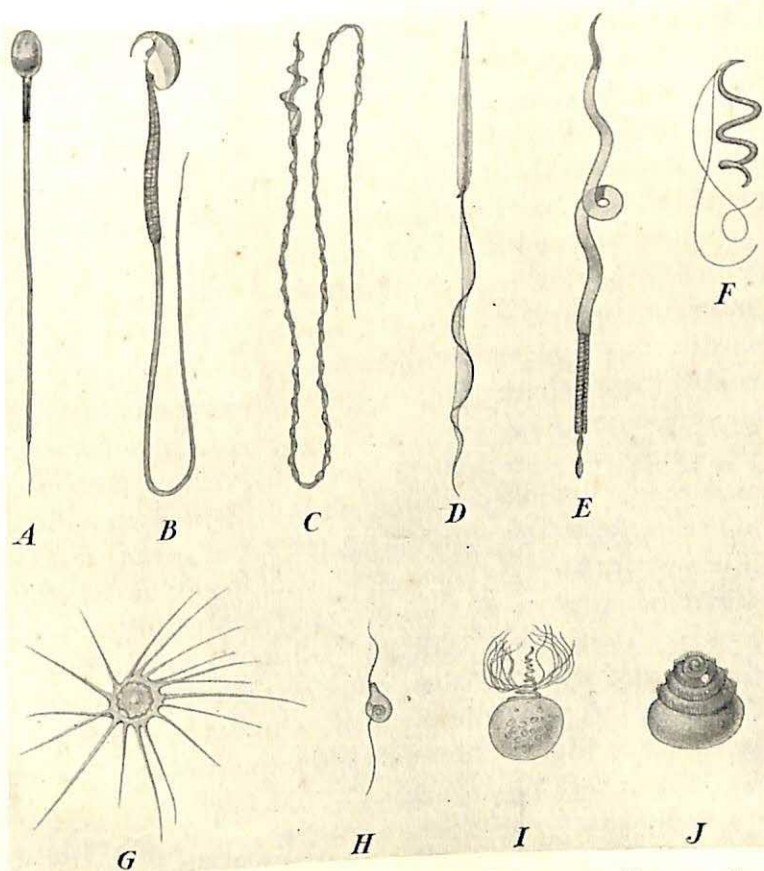


FIG. 10. A variety of sperms. A, man. B, the field mouse *Mus agrarius*. C, the bird *Chloris*. D, the toad *Bufo*. E, the skate *Raja* (showing only a small portion of the tail filament). F, the liverwort *Pellia*. G, the crab *Inachus*. H, the seaweed *Fucus*. I, the water fern *Marsilia*. J, the cycad *Zamia*. (Redrawn from Wilson's *The Cell in Development and Heredity*, after various sources. Courtesy of The Macmillan Company)

conical sperms with a large nucleus and a spiral band of cilia about the upper region of the cell. These sperms, though motile, are carried within the tip of the pollen tube as it grows out from the pollen grain and are never set free. In cone-bearing evergreens (gymnosperms) such as the pine and fir, the sperm has no spiral band of cilia, and in some cases the cell boundaries and cytoplasm also break

down, and the sperm is no more than a nucleus. This is the situation in all the flowering plants (angiosperms), the two microgametes in each pollen tube being simply nuclei.

Thus we see that there are regular transitions from the sperms of man to the microgametes of the seed plants. Male gametes differ in particulars, but invariably have one feature in common—the nucleus. There are many sorts of adaptations, presumably for entering the egg; and there are various devices for securing motility;² but the one structure which is to enter the egg, and which must be propelled toward it, is certainly the *nucleus*. This is the one common feature of all microgametes.

The megagamete, or ovum, is more like a typical cell. The animal ovum differs from that of the plant mainly in the presence of larger amounts of stored food, often of several kinds, and frequently of a number of complex envelopes, nutritive or protective.³ Within the ostrich egg, for instance, the ovum is crammed with yolk, distending it to such an enormous size that it is the largest of all cells. Around this yolk is an envelope of albumen (the white of the egg), around that a tough white membrane, really double, and finally the

² It is worth noting that the means of locomotion used by sperms are identically those possessed by single-celled organisms. Nonflagellated spermatozoa are either nonmotile or move slowly by cytoplasmic flowing. They thus resemble either the nonmotile sporozoans, diatoms, and desmids, or the rhizopods, such as the ameba and the radiolarians, with their flowing pseudopodia ranging from blunt, thick projections to long, delicate rays. Sperms with either one or two flagella resemble in their mode of locomotion the great group of flagellated unicellular organisms which lies in the borderland between distinctly animal and distinctly plant forms. The spermatozoa of toads and salamanders, with tails in the form of long undulating membranes, remind us of the trypanosomes. Finally, the ciliated sperms of the fern and cycad groups recall to us the thousands of ciliated infusorians, which often even have their cilia arranged in spiral rows like those of the cycad sperm. Without pressing resemblances too far, this is enough to show that isolated cells possess a few common means of locomotion: either by ameboid flowing and creeping, or by differentiation of vibratory cilia and flagella, or by an undulatory membrane. In discussing the course of differentiation in many-celled organisms, we shall find that their cells, too, employ the same devices. All life is united through these common potentialities of cell movement.

³ An ovum surrounded by nutritive and protective coats is known in animals as an *egg*, in plants as an *ovule*.

shell. The mammalian ovum is not as large as the eggs of other vertebrates. Surrounding it there is a layer of nutritive cells, the *corona radiata*, which is broken up and dispersed at the time of fertilization. The ovum itself is much smaller, 130-140 μ in diameter, so that it is just visible to the naked eye as a small speck. It is roughly spherical, and contains a large nucleus, in diameter one third to one fourth that of the cell. The cytoplasm contains only a moderate amount of yolk (Fig. 9A).

These differences are clearly associated with later needs of the embryo. During the long period of incubation, a developing bird must rely entirely on the stores of food and moisture within the egg, and must be protected from injury. On the other hand, a mammalian embryo very rapidly establishes a source of supply through connection with the body of its mother and, warmly sheltered within the uterus, needs less in the way of protection. This also explains the situation in the megagametes of the seed plants. Food is stored up for the developing plant, though in the surrounding layers and not in the ovum itself. Quite generally, then, stored food is present within ova, but its amount varies with that available elsewhere in the egg, and also with the length of the period during which the egg or ovule must depend entirely upon its own resources.

Inasmuch as the substances making up the stored food not only furnish energy for growth and development but also supply the components of the living substance itself, they include inorganic salts, water, and proteins, fats, and carbohydrates.⁴

⁴ In the hen's egg, the composition of the yolk is approximately:

Water	50%
Fats, lipoids and sterols	35%
Proteins	15%
Inorganic salts	1.5%
(Na, K, Ca, Mg, Fe, Si, SO ₄ , PO ₄ , Cl)	

Carbohydrates, except for a little free glucose, are lacking here, but in insect and mollusk eggs there is considerable glycogen. The relative absence of carbohydrates in eggs is what we might expect, for, in general, fats, which have

The ovum always contains a nucleus and a surrounding body of cytoplasm. In the latter are often structures which are thus directly passed on to the zygote. Plastids, for example, which are concerned with photosynthesis or starch formation in plants, are transmitted in this way to the offspring, and therefore stem entirely from the mother. In animal ova there are often pigment granules, and mitochondria and chondriosomes (granules and rods), which, there is evidence to believe, are seats of oxidative activity. Bacteria, filtrable viruses, and other parasites are also sometimes passed on in this way, as Pasteur found to be the case in the transmission of the "corpuscles" causing the fatal pébrine disease of silkworms.

We pass now to the several phases in the process of fertilization, the interesting features of which can be considered briefly, especially since we shall confine ourselves mainly to the events found to occur in animals. How does a sperm find its way to an egg? In one plant (*Fucus*) and perhaps in sea urchins, some substance secreted by the egg attracts sperms to it, but most attempts to demonstrate a chemical attraction between egg and sperm have been unsuccessful. Rather, the sperms seem to drive blindly about until they meet an ovum; or else, within a short time, they perish. In animals where fertilization is internal, there is, to be sure, a general guide in the nature of the passages traversed.⁵ Ova which are fer-

more potential energy per unit weight, are a better and more customary storage form than carbohydrates. The distribution of phosphorus in the yolk is especially interesting because it differs materially from that in differentiated cells. In the yolk there is a high proportion of lecithin and a characteristic phosphoprotein called *vitellin*; in tissues there is much less of these and the proportion of inorganic phosphates and of nucleoproteins is increased many fold. This indicates that in the cytoplasm the fats are used up to furnish energy, and that phosphorus-bearing proteins of a nutritive type, such as casein in milk, are broken down, transferred to the nucleus, and reconstructed in a form associated with chromosome activity.

⁵ Sperms make their own way up through vagina and uterus, swimming purely at random. But the uterine tubes are lined with cilia which set up a strong downward current against which the sperms are helpless. The walls of the tubes, however, are greatly folded, and the folds are continually altering their contacts with one another, so that temporary compartments

tilized in water often have a thick coat of protective jelly, which so increases their size that spermatozoa establish contact with them more readily. The mammalian ovum, as already mentioned, has surrounding it a layer of nutritive cells, which similarly increases its size.

Once a sperm meets an egg it appears to be entrapped, and so a large number of sperms are soon swarming about the egg. Wriggling vigorously, the sperms penetrate the outer coat of the egg. When this is a layer of cells, as in the mammalian egg, it seems to be dispersed by their activity. Some ova, such as those of insects or fishes, have only one point at which they may be entered by a sperm; others, such as the mammalian ovum, can be entered anywhere. In either case, sperms reaching the surface of the ovum become passive. A small cone then bulges from the ovum toward *one* of the sperms, and it is drawn into the ovum, usually in entirety, but in some cases leaving its tail behind; or even, as in the worm, *Nereis*, leaving its midpiece too. Evidently neither tail nor midpiece can be considered essential to fertilization, but only the head—that is, the nucleus.

Upon the entry of one sperm, fluid rapidly accumulates between the ovum and the toughening outer membrane of the egg. In eggs fertilized in water, this fluid is imbibed from the surroundings, but in mammals there is a very definite shrinkage of the ovum itself, which is thus so adapted that it depends upon its own supply of liquid. Every past change in the situation of the ovum, as of any cell, has necessitated certain corresponding changes in its own system. Or perhaps it would be better to say that changes in the genes controlling the cell system have made it possible for the cell to meet new situations more successfully! The instant result of the

form and reform. In the center of each temporary compartment the current flows up, so that some sperms will be carried to the upper end of a compartment and into the next, as the folds alter the positions of their contacts. Chance thus determines not only which sperms reach the upper end of the uterus, but likewise which are first successful in concluding their journey on up the Fallopian tubes to the egg.

changes just described is that all other sperms are prevented from obtaining entrance. Where the ovum is thus adjusted to the entrance of only a single sperm, poisons may cause the fertilization membrane to form so slowly that two or more sperms may enter. Development is always abnormal when this has occurred.

The membrane, however, is not the only insurance that one sperm and no more will participate in syngamy. A substance which diffuses out of mature ova, and which causes sperms swimming in water to clump together, ceases to be produced at fertilization or whenever the fertilization membrane is formed, whether by the action of the sperm or of various other agents (for example, butyric acid). The capacity of ova to be fertilized depends upon their content of this substance, which has been named *fertilizin*. The instant a sperm enters an ovum, some sort of chemical reaction between sperm and fertilizin sets up a block to further fertilization.⁶

We next find the sperm turning right about immediately after its entry. Developing about the centrosome in the mid-piece, when this enters, there appears an aster. The centrosome divides and gradually there is formed a typical spindle. The course of events from this point on is determined largely by the stage of the egg nucleus.

If the ovum is already mature (that is, if it has passed

⁶ In eggs which contain a great deal of yolk (insects, amphibians, birds, etc.) more than one sperm normally enters; yet only one actually takes part in syngamy, and the remainder degenerate. Here the block set up by the reaction is not to sperm-entry, but to participation in that fusion of nuclei which is the essence of the whole series of events. This situation also prevails in most plants, but in flowering plants (angiosperms) a peculiar variation is found. Here there are two microgametes, equivalent to sperms, in each pollen tube. Both penetrate the embryo sack, which contains, besides the megagamete and five cells destined to degenerate, two *endosperm* nuclei. One sperm unites with the megagamete, of course. The other, instead of disintegrating, as do supernumerary sperms in all animals and in the lower plants, fuses with the two endosperm nuclei, and the cell derivatives of the resulting triploid cell store up food for the developing embryo. This is the main foodstore in the seeds of monocotyledons, and since this group of plants includes all our cultivated grains, our principal food supply depends directly upon this double fertilization.

through the process of meiosis, to be described in the next section), the nuclei of sperm and ovum approach each other and fuse.⁷ The spindle grows, the fusion nucleus swells, and the chromosomes appear in it. The division which follows is typical.

However, if the ovum is not yet mature, fusion with the sperm nucleus is delayed until maturation has taken place. In this event the sperm head, while waiting, imbibes fluid from the surrounding cytoplasm, and swells into a typical interphase nucleus. Next the chromosomes appear, and pass through typical prophase changes, so that by the time the egg nucleus is ready to participate the sperm's chromosomes are ready to go on the spindle. The ovum's chromosomes then usually occupy one half of the equatorial plane of the spindle, and the sperm's the other; and no real mingling occurs until the daughter nuclei are reconstructed at the end of this cell division. The final result, however, is obviously the same as before.

To sum up: the essential feature of syngamy is the combination in a new individual of hereditary factors (the genes, located in the chromosomes) as a rule derived equally from two parents. Other essentials for growth and development (protoplasm containing food and cell structures) may be, and generally are, contributed entirely by one parent.

With one exception (see Chapter III, pp. 147-161), each gamete makes an equal genetic contribution to the offspring. For every chromosome contributed by the female parent in the ovum, a similar one is contributed by the male parent in the sperm, so that each chromosome possesses a "homologue." The genes in these homologous chromosomes must consequently be paired too and, while a gene may occasionally differ somewhat from its mate, in most cases they are undoubtedly identical. Here one may well raise a question:

⁷ That the two nuclei seen fusing in a fertilized egg are, respectively, those of egg and sperm and, hence, that the gametes are cells was demonstrated by O. Hertwig and by Fol, who were also among the six who determined the nature of cell division (pp. 12, 13).

Is it true that our inheritance is always half maternal and half paternal? Where our parents do differ as to some trait, will we of necessity be a blend between them? Here is a family in which the mother is brown-eyed and the father blue-eyed, and every one of the children resembles the mother. What about that? Evidently syngamy alone cannot explain the facts. What additional factor is then involved in the transmission of the genes?

IN THE MATURATION OF THE REPRODUCTIVE CELLS THE
CHROMOSOMES ARE SHUFFLED AND REDEALT IN SINGLE SETS

Each act of syngamy provides a zygote with two sets of chromosomes, one from the egg, one from the sperm. Then if all the zygotes are to be supplied with no more than two sets of chromosomes, this number of chromosomes (the *diploid* number) must be reduced somewhere in the course of the life cycle to the number of chromosomes characteristic of the gamete (the *haploid* number). When and how? To grasp the full significance of this is in fact to master the basis of hereditary variability in sexual organisms.

In animals, the halving of the chromosome number usually takes place during the formation of the gametes, in two cell divisions which differ characteristically from ordinary mitosis and, together, are called *meiosis*. It may seem that all that should be necessary to halve the chromosome number would be the suppression of the duplication of the chromosomes in some one mitosis. But we should not forget what was pointed out in Chapter I, that *every* gene (and hence every chromosome) is essential to the normal functioning of each cell. No merely random sorting of the chromosomes into two numerically equal groups could, therefore, provide complete *sets* of chromosomes as a regular occurrence. Accordingly, we should expect some additional process to accompany the suppression of chromosome duplication, some process which would insure that each chromosome would be

allotted to a different set from its homologue. Is this to be found in meiosis?

As we observe prospective sex cells becoming mature, we can notice that they first become different from other unspecialized cells by passing through a prolonged period of growth, during which a large store of food is accumulated in the cytoplasm of each one. This is much greater in the potential eggs than in the cells which will produce sperms, but it is present in the latter, too. While this storage is going on, each chromosome, already doubled as usual for the next cell division, pairs up side by side with its homologue, so that there appear to be only half as many chromosomes as previously, while each one is clearly made up of four strands. (It is often called a *tetrad* while in this association.) This intimate pairing of homologous chromosomes, one of paternal and the other of maternal origin,⁸ is known as *synapsis*. It endures for a considerable length of time, so that the prophase of this first division of meiosis is greatly prolonged. Later we shall see that synapsis affords an important opportunity for the homologous chromosomes to exchange genes, but for the moment we shall notice only its effect upon the disjunction of the chromosomes.

As the chromosomes become attached to the spindle, they are still paired. *Separation then follows, not between the strands of each individual chromosome,⁹ but between the paired homologues.* The two cells resulting from this division, therefore, each receive one chromosome from each pair, and thus get a complete set of already double chromosomes (see Fig. 11). In the second division, each chromosome is already double, *and the usual duplication is suppressed.*

Meiosis thus requires two divisions, each of which dif-

⁸ The demonstration that the chromosomes which pair are, respectively, of maternal and paternal origin is basic to the Chromosome Theory of Heredity, which has in turn formed the essential framework of modern genetics. It was made by T. H. Montgomery, University of Texas cytologist, in 1901, just after the rediscovery of Mendel's work.

⁹ The term *chromatid* is used to designate a single strand of a split chromosome or of homologous paired chromosomes.

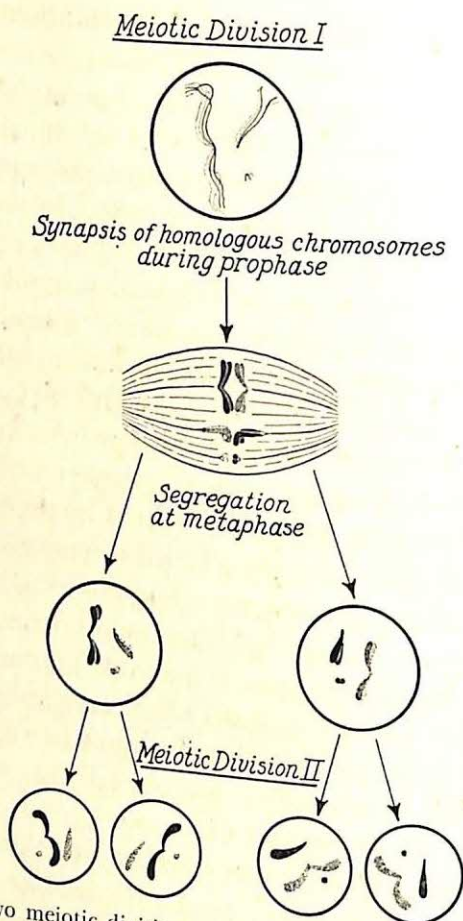


FIG. 11. The two meiotic divisions. The original paternal chromosomes are shown shaded; the original maternal chromosomes in solid black. The different pairs of chromosomes are distinguishable by their shapes and sizes, as corresponding maternal and paternal chromosomes are alike in these respects.

fers from an ordinary mitosis. In the first division, there is the pairing and then the segregation of each chromosome and its homologue. In the second division, its initial phase, the duplication of the chromosomes, is inhibited. As a consequence, four cells, each with a haploid chromosome number, are produced from every potential reproductive cell which enters meiosis. How these haploid cells then become gametes will be related in Chapter III.

We can now ask ourselves what benefit, if any, is conferred upon sexual organisms by the existence of syngamy and meiosis. What advantage does a diploid constitution apparently have over a haploid? This we can discern by considering a certain ameba (*Ameba diploidea*) and some of the fungi (Ascomycetes, e. g., *Pyronema*). In the ameba, for example, two individuals conjugate, much as in the familiar process in *Paramecium*. A bridge of protoplasm is formed between them and, following meiosis, a haploid migratory nucleus from each crosses into the other, where a similar haploid nucleus has remained. When they separate, each individual therefore has two haploid nuclei, of different origin. Instead of fusing as they commonly do in other protozoa, in this ameba these two haploid nuclei remain side by side, dividing synchronously. To all intents and purposes the essential function of syngamy, that of bringing together in one cell nuclear material of different origin, is therefore fulfilled. The ameba is diploid, and not haploid, through its life cycle. Yet when it prepares to conjugate again, the two nuclei first fuse, to be followed immediately by meiosis. This case—that of the fungus is essentially the same—is highly illuminating. *It shows that the advantages of a diploid constitution, whatever they are, depend only on the presence within the cell of the two sets of chromosomes, although for meiosis to occur these must be in the same nucleus.*

Now just what feature of meiosis could occur only if the chromosomes of maternal and paternal origin are included in the same nucleus? Obviously, the pairing of the homologous chromosomes—and, subsequently, their disjunction—could occur only if this were the case. Have we noticed all the consequences of this? If we glance at Fig. 11 again, we can see three pairs of chromosomes, one pair of big V's, one of medium-sized rods, and one of very small globules, shaded so as to distinguish those of the original paternal set from those of the original maternal set. But the sets of chromosomes sorted out into the gametes are not necessarily these same

original sets; that is, *the original paternal and maternal contributions are shuffled before they are redealt to sperms or eggs*. Each gamete carries a complete set of chromosomes, for it gets one member of every pair, but without regard to whether they came originally from parental sperm or from parental egg.

This shuffling results from the fact that each pair of chromosomes takes up its position on the spindle independently of all the others. When disjunction occurs, *A* disjoins from *a*, its homologue, *B* from *b*, and so on. But *A* can go toward either pole, provided *a* goes to the opposite one; and *B* and *C* can also go toward either pole. Then *A* can go either to the same pole as *B* or to the opposite; so too it can go either with *C*, or opposite to it. In other words, *the members of different pairs recombine at random*, and all possible combinations will occur with equal frequency. There are eight of these, of which only two (*ABC* and *abc*) are the same as the parental combinations. The others are recombinations of the chromosomes, and hence of the genes in them. If we consider in addition a fourth pair of chromosomes, its two orientations on the spindle will make two combinations with each of the previous eight, that is, sixteen in all. But of these, again, only two will be the original parental combinations—the rest will be recombinations.

These results may be summed up in a simple formula. Each pair can be oriented two ways; then 2^n gives the number of combinations, where n is the number of chromosome pairs.

2 pairs	$2^2 =$	4 combinations
3 pairs	$2^3 =$	8 combinations
4 pairs	$2^4 =$	16 combinations
n pairs	$2^n =$	number of combinations from n pairs

For ourselves, with forty-eight chromosomes per cell (twenty-four pairs), the number of combinations is therefore 2^{24} . Of all these (16,777,216), only two resemble the original parental combinations exactly. The chance of a human gamete re-

peating either of these is therefore only one in 8,388,608. The odds indeed favor a new deal!

We may carry this analysis a step further. Common conceptions of heredity trace one half of each person's characteristics to each parent. While this is not true, as we shall see later, it is a fact that each of us receives one half of our chromosomes from each parent. Can it be true, as common ideas also conceive, that one fourth of one's heritage comes from each grandparent, one eighth from each great-grandparent, and so on back? Not in the least. There is one chance in 8,388,608 that not a single chromosome of ours was derived from a particular grandparent, and there is almost one chance in 300 that his contribution consists of no more than five chromosomes of the twenty-four in the set we receive from the parent on his side. For great-grandparents the likelihood of proportionate contribution to any single descendant's heritage is even less; and of one's sixteen great-great-grandparents, there is better than an even chance that some one of them will not be represented in our heritage by a single chromosome. This takes us back only four generations. With two more, we shall reach a generation in which we had more ancestors than chromosomes, so that we cannot possibly have inherited whole chromosomes from all of them. Now, as we shall find out later, there are more hereditary units than there are chromosomes, for chromosomes do not always behave as indivisible units in transmission (pp. 107-118). However, these hereditary units, the genes, are limited in number to probably not more than 10,000 or 20,000, so that a mere five hundred years ago we must have had many an ancestor from whom we have failed to inherit so much as a single gene.¹⁰ This news, however,

¹⁰ It should be pointed out that, wherever inbreeding has been extensive, the number of ancestors is consequently less than 2^n at any n th generation. This would somewhat increase the chance of inheriting from each ancestor, though not to any considerable extent in human stocks where extensive outbreeding is the rule.

should be kept private, lest it greatly dishearten all those interested in genealogies and pedigrees.

The number of possible combinations in the offspring of any pair is the *product* of the number of possible combinations in their sperms and eggs, that is, $(2^n)^2$. For us, this amounts to the staggering total of 281,474,976,710,656. It is easy to see why no two individuals produced from separate fertilizations ever chance to be identical.

It is also interesting to reflect on the amazing odds against our ever being just the combination we turned out to be, with 281,474,976,710,655 chances to 1 against it. We are amazed when an acquaintance happens to win the grand prize in any such huge lottery as the Irish sweepstakes, but that chance is enormous compared with the inconceivable chance that we should be just what we are.

Meiosis, then, has significance for heredity, not so much because the chromosomes are reduced in number, as because in the process they are thoroughly reshuffled, and an almost limitless variety of new combinations of the hereditary factors results. In drawing these conclusions, to be sure, we have been making one important assumption—that every chromosome differs not only from all the chromosomes of every other pair, but also from its own homologue, in at least one respect. We should never obtain different hands (that is, recombinations) if our cards were all alike, no matter how much we shuffled them. As we estimate our hands according to the differences of the cards, so our knowledge of the hereditary pattern rests upon differences between genes, upon whatever differences there may be between the two members making up each pair. It is true that, for most pairs, the members are alike. Only occasionally do they differ. Yet all we can learn of the pattern directly, we must learn from those occasional differences between *alleles*.¹¹

Now of the several possible states in which each gene can

¹¹ The two partners of any pair of genes are *alleles* (allelomorphs) of each other; in a broader sense, any genes which can become partners when brought together by syngamy are alleles.

exist, not all are equally advantageous; some will be relatively deleterious. Since the genes are paired, any control over the processes of development exerted by a given gene is, to some extent, modified by its partner. If, then, one of the two is deleterious, the harmful effect is generally partly, and often even wholly, counteracted by its allele. *The diploid constitution therefore provides insurance against any deleterious effects exerted by genes.* On the other hand, a haploid cell carries only one gene of each sort, and there can be no counteraction of harmful effects if deleterious genes are present. Here the sinning gene has no good angel to atone for its evil action!

This life and accident insurance is the great contribution of syngamy, over and above its contribution to individual variety. Yet we have answered one question only to raise another. We have now to look into the problem of the origin of varieties of alleles.

HEREDITARY VARIATION ARISES PRIMARILY FROM PERMANENT CHANGES IN GENES

Cell division begins with a duplication of each gene. As long as genes are derived from pre-existing genes, all representatives of any particular gene will therefore be alike. Nor is it possible to assume, as some early geneticists did, that all hereditary variation is simply the kaleidoscopic recombination of original differences present in the progenitors of each species. This is not possible, because some genes are known to exist in a considerable number of different states, and we must accordingly either give up the postulate of a single origin or admit that genes, although regularly the most stable of living units, may occasionally alter.

Variation, as we observe it, would be impossible were the genes immutable. While retaining their ability to duplicate themselves during mitosis, they must be able to mutate. Can this be observed—perhaps even produced artificially?

Most of the unusual variations we see for the first time are not really new at all, but are reappearances of old traits which come to light through the recombinations of genes resulting from mating. The first true mutation to be recorded in an animal appeared in a male lamb in the flock of Seth Wright, Massachusetts farmer, in 1791. This lamb had very short bowed legs, and from it was bred the Ancon sheep, a breed so short-legged they were unable to jump the low

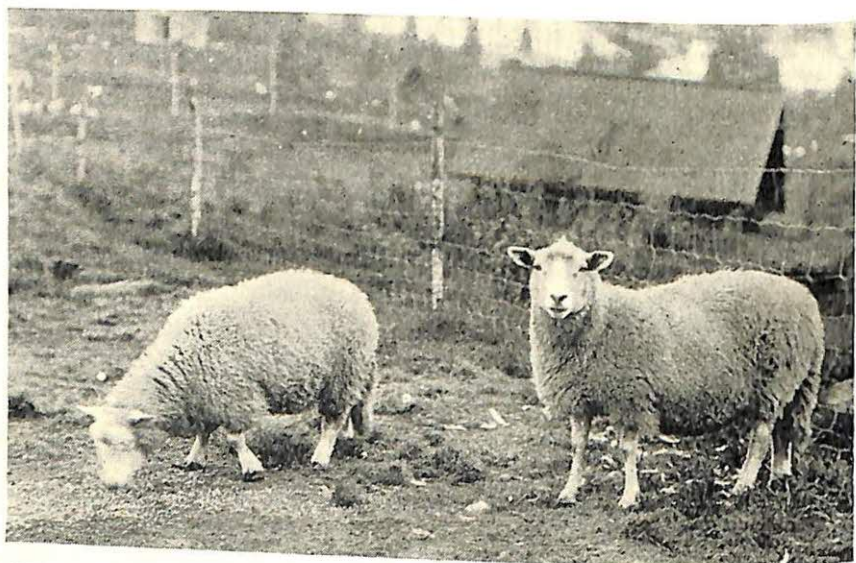


FIG. 12. An Ancon short-legged sheep beside a normal sister. (Courtesy of Department of Genetics, Agricultural Experiment Station, Storrs, Connecticut)

stone walls around sheep pastures. The same mutation later appeared a second time, in Norway, after the early breed had become extinct (Fig. 12). Other examples of spontaneous mutation have been the appearance, in the Florida velvet bean, of a new variety able to flower and fruit anywhere in the south of the United States, instead of being limited to Florida and the Gulf region; and the appearance, in tobacco, of a new variety able to flower only when day and night are proportioned as in the subtropics, instead of as in Kentucky or Virginia, home of the parent variety.

What are undoubtedly mutations have occurred in human populations, too, although we cannot be so precise as to the exact date. For example, there is a peculiar kind of woolly hair, oval in cross section instead of round like ordinary hair, and with thin places where it breaks easily. This makes it not only woolly but also "self-bobbing." (It is, however, not identical with the kinky hair of Negroes.) In 1786 there was born, of Norwegian farmer stock, a girl who had this woolly hair, and she has now had four generations of descendants, of whom many have had the same kind of hair. Whether the mutation first appeared in her, or in some earlier, unrecorded ancestor, we cannot say. The same trait, or one very like it, has been traced back for five generations in the little village of Rijnsburg, near Leiden, Holland; it has also turned up in our southern states. Perhaps these cases are of common origin, and the original mutation occurred many centuries ago. More likely, the mutation has occurred two or three times and maybe, in one of the cases, as recent as the eighteenth century.

The scientific study of gene mutations began in 1910 in the laboratory of Thomas Hunt Morgan at Columbia University. One day, among the hundreds of ordinary red-eyed fruit flies in a culture bottle, a single male fly with white eyes was discovered. From this mutant fly a race of white-eyed flies was bred, and by crosses with the normal red-eyed flies the hereditary behavior of the new gene was determined. The great search was on! During the next seventeen years more than 15,000,000 flies, mainly from purebred stocks known to be free from mutations, were scrutinized for new forms. In this way about 500 mutations were found. There were flies with altered eye color—pink, brown, sepia, purple, orange, and many other shades; there were flies with the regular rows of eye facets disarranged, with the size of the eye diminished; there were even flies with no eyes at all. There were types with wings bent or curved, held outstretched from the body, blistered, scalloped, nicked, short-

ened, or entirely gone—poor creatures able only to hop or crawl about. Others were Negroid races, or “Nordics,” of a light yellow body color instead of the ordinary gray. Still others had bristles appearing snipped off, or close-shaven. And in one mutation the antennae on the head were actually replaced by what looked like legs! Many of these changes, of course, were so drastic that the mutant individuals were feeble, dying young, unable long to survive the competition of normal flies bred in the same bottle.

All this might lead us to think that *Drosophila* is especially subject to mutations of its genes. But when we recall that almost a score of millions of flies were examined to find these 500 mutants, the fruit fly does not seem so very mutable after all. On the contrary, *most genes are extremely stable*. Although their individual mutation rates vary considerably, with few exceptions all the rates are extremely low.

Not all mutations, of course, produce changes in the organism visible to an observer looking only upon the exterior.¹² Many morphological changes will be entirely internal, and these will very likely be of even greater importance to the animal or plant than superficial, readily observed changes. Moreover, structure is but a means to function and is itself a product of function—the creation of physiological processes. Mutations that alter structure must do so by altering these processes. Other changes in physiology may be unaccompanied by changes in visible structure. To estimate their frequency we can look for alterations in “viability” and “fertility.” If we compare the proportion of flies of one type which successfully emerge as adults with the proportion of some standard type hatching in the same culture,¹³ and if

¹² One reason the fruit fly has been so favorable an object for genetic study is that since, like all arthropods, it has an external skeleton, the proportion of mutations with externally visible effects is higher than in forms like vertebrates, which have a relatively undifferentiated exterior.

¹³ This point is essential. If environmental factors were not identical for our two types, differences might be attributed to them rather than to genetic make-up. In scientific experiments all factors except the one whose effects are being tested must be kept constant.

any difference between the types is inherited, we can speak of a genetic difference in "viability." If we compare the frequency of hatching eggs from matings of two types of males with the same females, or from two types of females mated with the same males, we can similarly measure any genetic difference in "fertility." If we have started with types of known viability or fertility, and then we detect an inherited difference in these respects in the course of further breeding, we can attribute it to a mutation.

In the completest analysis of this sort yet made, it was found that mutations which lower the viability somewhat (up to 15 per cent), but do not produce any externally visible effect, form the most abundant group, making up almost two thirds of the total. They are about twice as frequent as those mutations which reduce the viability so much (70 per cent or more) that they usually cause death. These are called *lethals* or *semilethals*. They sometimes involve visible deformities, but often, in the occasional individuals which do survive, have no obvious external effect. The mutations which markedly alter the appearance practically always have a somewhat reduced viability, too. They are extremely infrequent, however, as compared with the other two groups, being at most $1/25$ as common as the lethals. As for beneficial mutants, they are the rarest of all, scarcely amounting to so much as one third of 1 per cent of all mutations; only one turned up among 356 mutations in this experiment. *Most mutations in the fruit fly, we can conclude, produce no visible external change and are deleterious.*

Turning to mammalian heredity, we can find plenty of mutants of definitely deleterious effect, many that are lethal. The generalization just made is by no means limited to fruit flies! Many such mutants, for instance, have been described in cattle, chiefly those which kill the calves late in prenatal development or shortly after birth; for these are most readily detected. The "parrot-beaked" calf has an abnormal lower jaw with impacted molar teeth, a condition resulting in death

a few hours after birth. "Amputated" calves have neither limbs nor lower jaw; they are born dead. "Elk-calves," on the other hand, have normal legs and jaws, but an extremely shortened spine and trunk; these, too, are stillborn. "Bulldog" calves (Fig. 13) have extremely short legs, a dumpy build and scooped-out faces like those of human achondroplastic dwarfs; they are known in two forms: one always stillborn,



FIG. 13. A "bulldog" calf from the Norwegian Telemark breed. The malformation of its spinal column and legs is due to a recessive lethal gene. (From Mohr's *Heredity and Disease*. Courtesy of W. W. Norton & Co.)

the other (less extreme) managing to live a few days. These by no means exhaust the list.

In man there are many similar examples, ranging all the way from conditions lethal before birth to those only mildly disadvantageous. Extreme lethals include certain malformations of skin, limbs and jaw, and brain-case (Fig. 14). Lethal during relatively advanced development are such hereditary degenerative diseases as Wilson's disease and Huntington's chorea, a form of "St. Vitus's dance." Detrimental, but not necessarily lethal, are congenital absence of hands and feet (Fig. 15), hemophilia, harelip and cleft palate, and numerous other genetic conditions. Finally, some mutants, such as polydactyly or the woolly hair mentioned earlier, are not obviously detrimental.¹⁴ Other genes may even be advanta-

¹⁴ There is a discussion of representative hereditary diseases and lethal conditions in man in O. L. Mohr, *Heredity and Disease*, Chap. IV, Sec. 1-3 (W. W. Norton, New York, 1934). The medical terminology lends a false ap-

geous. In the tropics those that produce quantities of melanin (black pigment) in the skin would probably be so. But, of course, we have no measure of the frequency of these different sorts of mutation in man. We must turn to *Drosophila* for that.

Even in *Drosophila* we would know little of mutation rate, especially of the different categories of effects, were it not for the discovery by H. J. Muller in 1927, at the University of Texas, that *mutations can be induced at a high rate by subjecting the genes to x-ray bombardment*. Treatment, within such limits of severity as flies can stand, will raise the mutation rate from the low spontaneous level previously described to two or three mutations per individual!

This is an increase of about one hundred fold! At the same time, the genes go on mutating in the same respective proportions, without any differential effect of the treatment. Hence, it is practicable to make comparisons of the different sorts of mutation (advantageous, slightly detrimental, semilethal, and lethal), and the experiments on viability just described made use of this technique.

The use of radiation to increase the mutation rate has yielded nearly all our information about mutation, and from the study of mutation we have learned much of what we know about the nature of the gene. We will not go into the



FIG. 14. "Amputated" abortion. The parents were first cousins. (From Mohr's *Heredity and Disease*. Courtesy of W. W. Norton & Co.)

pearance of difficulty to the discussion. See also *Heredity in Man* by R. R. Gates (Macmillan, New York, 1931) and the graphic popular presentation, *You and Heredity*, by A. Scheinfeld (Stokes, New York, 1939).

nature and cause of the mutation process here, for we are concerned mainly with the nature of the gene as it bears upon the processes of development. We will therefore summarize briefly



FIG. 15. A dominant mutation resulting in the congenital absence of hands and feet. The mother of the family is normal, but her husband, like his three children and brother in the picture, lacked hands and feet. (Courtesy of O. L. Mohr)

what has been learned about the gene through the study of mutation.

We have already seen (1) that most genes are extremely stable; (2) that mutants are frequently devoid of visible effect; (3) that most mutations are, to a greater or less degree, deleterious. To these we may add:

(4) *Mutations may occur at any time in the life cycle.* Mutations are not limited to reproductive cells, but may occur in somatic tissue, making mutant areas of a size corresponding to the number of descendant cells produced. Evidence that the physiological state of the cell affects the muta-

tion rate is still inadequate, but it is possible that this may turn out to be of very great importance.

(5) *A mutation of a gene may consist of either its loss, its change, or a loss or change of its neighbors.* The first is known from the fact that many lethal genes in the fruit fly can be shown, by cytological observation of the giant salivary gland chromosomes, to involve actual deficiencies of small parts of the chromosome. The second can be shown indirectly by cytological study, too, through an absence of any detectable loss or rearrangement within a giant chromosome carrying a mutation, but is shown more convincingly by the ability of many visible mutants to mutate back to their original states. The third is shown by the fact that certain genes, even though they experience neither loss nor change themselves, mutate when they are removed from one neighborhood and brought into juxtaposition with new neighbor genes. All this is extremely important, for we detect genes by their differences from their alleles, and these differences have arisen by mutation. Since mutation includes several phenomena, it is illogical to assert that we consistently mean any one thing at present by the term gene.¹⁵

(6) *A given gene may become altered in more than one way.* This goes further than the preceding conclusion, as it refers to the multiple variety of those reversible changes which are neither losses nor "position effects." Here we mean that a particular gene may have more than one sort of allele, and that the effects of these alleles may vary quantitatively or qualitatively. The number of possible changes varies with each gene, so that series of such "multiple alleles" run to different lengths. The number of alternative combinations involving one or another allele of such a multiple series adds enormously to the possible variety of the hereditary pattern, and will be discussed in the next section.

¹⁵ This is often misunderstood. In theory we often define a gene as a unit in the chromosome. In practice we always identify a gene by its effects, hence, confusion.

Hereditary variation is primarily due to these alterations of the genes. Their appearance in various combinations—in other words, the emergence of various sorts of individuals—is, however, due to the mechanism of syngamy and meiosis. We have now to see how the pattern is made up.

POTENTIAL VARIATION IN THE INDIVIDUAL HEREDITARY PATTERN
IS A DIRECT CONSEQUENCE OF THE NATURE OF
MEIOSIS AND SYNGAMY

We have found that the significance of meiosis for heredity lies in the recombination of the hereditary factors, the genes, which it brings about. Syngamy makes the variety of possible combinations vastly greater. From the chance shufflings of the chromosomes in reduction and the random mating of gametes, each of us emerged as one of 281,474,976,710,656 possible types our parents could have produced, a number that is more than 100,000 times the present population of the earth.

It is mentally impossible to follow such permutations as these. No wonder many a biologist of the nineteenth century felt that the nature of heredity was doomed to remain an insoluble perplexity! But after all, we do not need to know the course of each thread to understand how a great tapestry is woven. The pattern of heredity can be readily comprehended by tracing no more than two or three of the "threads" which make it up. It was Mendel who showed us this truth. The work of Mendel, at first completely ignored, has become in our present century the foundation of the tremendously increased knowledge of heredity that man now possesses.¹⁶

¹⁶ Gregor Johann Mendel, born in Silesia in 1822, was the son of a peasant farmer whose study of fruit-tree grafting engendered the first interest in genetics in his young son. Mendel's education involved great sacrifice by his family, a younger sister even giving up part of her dowry that he might finish the *Gymnasium* (high school). On graduating, he entered the Augustinian monastery at Brunn, probably as a result of the influence of a

Mendel was clear-sighted enough to see that it was hopeless to try to work out all the intricacies of heredity at once. He determined to test the inheritance of no more than a single pair of contrasting characters at a time. Working with garden peas, he selected such alternative traits as tallness versus dwarfness, red flower color versus white flower color, green versus yellow seeds, smooth versus wrinkled seeds, and so on, for different tests. Instead of restating his results, which can better be gotten direct from his own paper, we shall take a human trait as our example, it having been well established by now that practically all hereditary traits are handed down in the same fashion.

Probably all of us have heard of albinos, people with a complete lack of pigment in the skin and outer layer of the body, including the eyes. They are a dead-white, hair and skin, and have eyes that appear pink, since, with no pigment

teacher who was a monk of that order. He attended the University of Vienna for two years, at the expense of the monastery, and then returned to Br \ddot{u} nn to teach physics. While making a reputation as a good teacher, he carried on his famous plant-breeding experiments. After eight years the experiments with peas were completed, and in 1866 he communicated them to the Society at Br \ddot{u} nn, where they aroused little remark. Three years later the paper on hawkweed (*Hieracium*) hybrids suffered the same fate. Copies which were sent to N \ddot{a} geli, the leading geneticist of the time, were treated no better. Despondency ensued, and Mendel published no more. The results of his vast experimentation with bees seem forever lost to us, as even the notes have disappeared. Elected prelate of the monastery in 1868, he became embroiled with the Austrian government over religious taxation, advocated "passive resistance," and resisted to the last. "From being a cheerful, friendly man," says William Bateson, "he became suspicious and misanthropic." The last ten years of his life were passed in disappointment and bitterness. Often he said, "Meine Zeit wird schon kommen" (My time is coming). Sixteen years after his death in 1884, his day did come, when three great breeders, Correns, deVries, and von Tschermak, simultaneously confirmed his results, and published to the world his enduring fame.

There is a good full-length *Life of Mendel*, by Hugo Itlis (W. W. Norton, New York, 1932). There is also an excellent biographical sketch of Mendel by William Bateson, the English geneticist, in *Mendel's Principles of Heredity*, together with portraits made in 1862 and 1880, and full translations of the papers on peas and hawkweeds. (Cambridge University Press, 1909.) The paper on peas should be read by all persons interested in genetics. It is a masterpiece of scientific writing describing a masterpiece of scientific experimentation.

in the iris, the red of the blood in the numerous fine blood vessels of the eye shows up.

Albinism is found in practically all vertebrates. We have all seen white rabbits, rats, and mice that have pink eyes; but albino deer, squirrels, weasels, porcupines, alligators, rattlesnakes, frogs, fish, and numerous birds, such as peacock, turkey, crow, robin, and sparrow, also occur. Literature, too, presents the classic example of "Moby Dick," the albino whale. In all these forms it seems probable that the trait is due to the same gene. In other words, this is one of the genes we share with lower forms of life, a reminder that *not all genes possessed by man are "human" genes.*

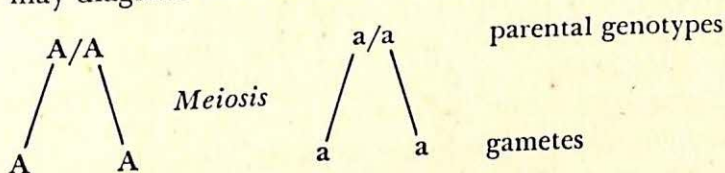
Let us, then, breed a pair of mice, one of them of the ordinary wild gray type, the other a "white" (albino). When their first litter is born, we discover that all the offspring are like the gray parent—and no matter how many such crosses we make and how many litters we raise, this is the only kind we shall ever obtain, barring mutation. All the first generation (F_1) are uniformly gray.

Now if we mate these gray (nonalbino) mice of the F_1 together, what will we get? Some of the litters will contain white mice! And if we raise several dozen such litters, and notice how many of each kind there are in all, we shall find that there are about three times as many gray (nonalbino) mice as albino ones. And the more such litters we raise, the more exactly will we find that this ratio of 3 : 1 is obtained. How can we explain it?

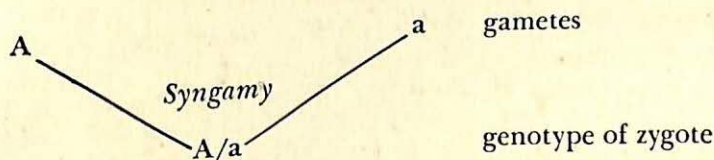
To begin with, it is evident that the albino trait has reappeared after "skipping a generation," so that whatever factor is responsible for it must have been carried by the gray mice of the first generation of offspring, along with the factor responsible for their grayness. One of these factors must dominate the other, so that, although both are present, only one, the dominant, is expressed, while the other is recessive.

These factors we now call *genes*. Since, as we recall, sperm and egg each contribute a set of these genes to the individual

through syngamy, and consequently every gene in one set has a partner, or allele, in the other set, we may represent those concerned here by a pair of symbols, A for the dominant (nonalbinism), a for the recessive (albinism).¹⁷ If we started with gray and albino mice of pure stock, their *genotype* (genetic constitution) was A/A and a/a . What happens to these pairs of genes at meiosis? The homologous chromosomes, and hence the genes within them, first pair and then disjoin. In the gametes of one parent, then, A will have disjoined from A , and every gamete will carry A . In the other parent a will disjoin from a , and every gamete will carry a . We may diagram this as follows:



There is only one sort of ovum here, and only one sort of sperm. Hence, at syngamy, an ovum carrying A is necessarily fertilized by a sperm carrying a ; and the resultant zygote is A/a . Finishing our diagram:

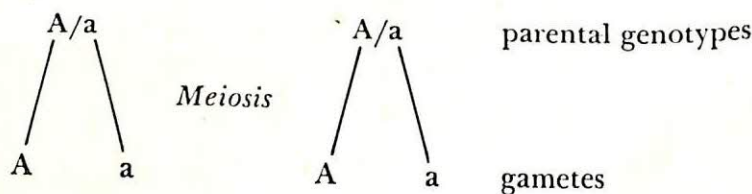


¹⁷ At this time it will be well to become acquainted with the essentials of the geneticists' symbolism, which we shall need to use repeatedly. Letters are used to represent individual genes, with the dominant allele capitalized and the recessive a small letter; or the mutant allele is given a letter symbol, and the "normal," i.e., wild type, allele has the same symbol with a "+" superscript. Thus A and a are dominant and recessive alleles, or a^+ might be used for A , since here the dominant is the normal allele. A dominant mutant, such as Bar (p. 110), has the symbol B , and its recessive wild-type allele is B^+ . Since alleles are carried in homologous chromosomes, a genotype is written with one bar (or two) between the alleles, e. g., A/a ,

$\frac{A}{a}$, or $\frac{A}{a}$.

The genotype of the zygote is not like that of either parent, for the two genes of the pair we are following are now unlike. The zygote is hybrid, not pure; or, to use the convenient terms of the geneticist, the parents were *homozygous*, but the offspring is *heterozygous*. We should note another fact about the offspring of this mating. Since the only combination of gametes is A with a , all the offspring, no matter how many, will have the genotype A/a . They will all be heterozygous! And they will all be alike! Or to generalize, we can say that when parents differ with respect to some trait for which each is pure (homozygous), their offspring are all heterozygous and uniform. In the present case, since A dominates over a , the heterozygous A/a offspring will be uniformly nonalbino, and experience shows that this is really so. But even where there is no dominance, as we shall see, the rule holds true.

Now see what happens when two such heterozygous individuals mate! First—meiosis; then—syngamy:



This time, when we come to syngamy, we can see that there are a number of possible combinations. We can best keep these straight by using the so-called checkerboard method, listing the gametes of each parent along one side, and filling the squares with the appropriate combinations:

		sperms		
		A	a	
ova	A	A/A	A/a	Syngamy
	a	A/a	a/a	

Result: Three different genotypes, in the ratio $1 A/A : 2 A/a : 1 a/a$. The offspring of heterozygous parents comprise two heterozygotes to one of each homozygous type. Since A is dominant, the heterozygotes here will be nonalbino, resembling the homozygote A/A , so that there will be three non-albinos for each albino. This 3 : 1 ratio is the *phenotypic*



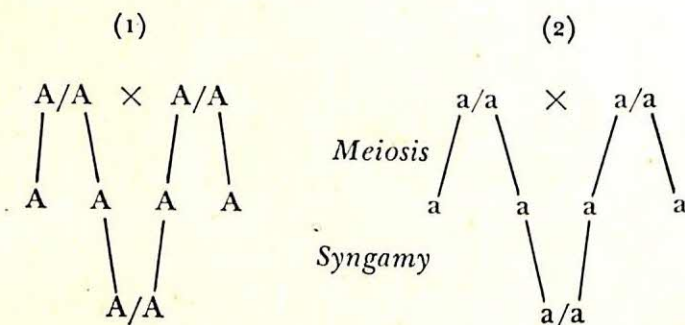
FIG. 16. Albinism in man. Normal parents with three albino children and four normal. (Courtesy of O. L. Mohr)

ratio. It states the relative frequencies of the offspring when classed by their traits *as expressed*. However, when we come to predict the results of various sorts of mating, it is always the *genotypic* ratio that must be made the basis of our analysis.

The family shown in Fig. 16 illustrates what we have been saying. "As seen from the picture both parents are perfectly normal. That they nevertheless carry the recessive gene is evidenced by their offspring. This fundamental relation, that a strictly hereditary anomaly may be transmitted through

perfectly normal individuals, has been the cause of much misunderstanding. And still many people stick to the entirely wrong conception that only those anomalies are hereditary which manifest themselves *both* in parents and in offspring. Nothing could be more erroneous.¹⁸

Have the A and a genes been altered in any way by their association throughout the parental generation? Not at all! The A/A and a/a offspring are like their grandparents. The a/a offspring are just as pure albino as the original strain before hybridization and, as our next example shows, breed as true. If we mate A/A with A/A and a/a with a/a , each cross yields only one possible type:



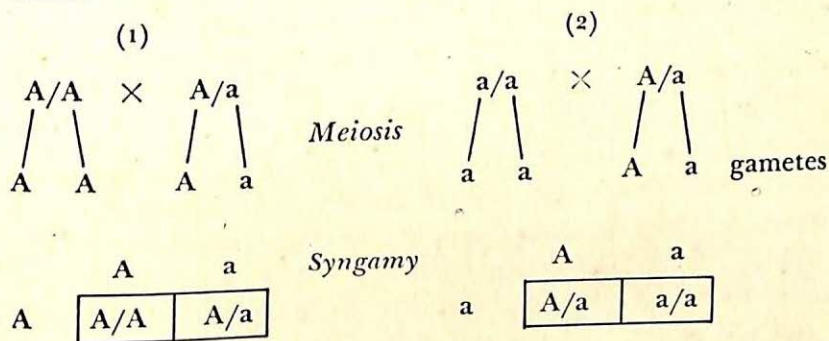
Result: Matings between similar homozygotes yield only homozygotes of the parental type.

If we look back at the cross between two heterozygotes, we are reminded that one fourth of the offspring are homozygous A/A and one fourth are a/a . The crosses just diagramed thus indicate what results we can expect if an individual of either of these homozygous groups is mated with its like. One half of the offspring of the A/a by A/a cross will give rise, upon mating with their like, to pure lines, A/A and a/a . The other one half, heterozygous like their parents, will, when bred within their own group, naturally repeat the same ratio in their offspring, 3 nonalbino : 1 albino—or by geno-

¹⁸ Mohr, O. L. *Heredity and Disease*, pp. 64-65. W. W. Norton, New York, 1934.

types, 1 homozygous nonalbino : 2 heterozygous nonalbino : 1 (homozygous) albino. The results thus far are summed up in Fig. 17. These parallel the fundamental facts found by Mendel in his crosses with peas, using seven different pairs of contrasted characters. His results led to the conclusion that *inherited characters are due to units which are paired in the organism but segregate in the formation of the gametes, the latter therefore being pure. The factors have not been affected by their association.* This is the first, and most important, Mendelian law of inheritance.

We can make one other type of cross involving these genes. The heterozygous type can be mated with either homozygous form:



The cross A/A by A/a gives us the ratio 1 A/A : 1 A/a , that is, one homozygous dominant to one heterozygote; phenotypically all will be nonalbino. The cross a/a by A/a , on the other hand, gives us 1 A/a : 1 a/a , that is, one homozygous recessive to one heterozygote; or, half nonalbino and half albino.

When can a purely recessive trait, such as albinism, show up? Obviously, from our diagrams, only when both parents carry the gene for it. Then, should the parents both be heterozygous, it will show up in one fourth of the children. This explains why "*consanguineous marriages favor the appearance of recessive traits.*"²¹ Closely related people, since

²¹ Mohr, *op. cit.*, p. 26.

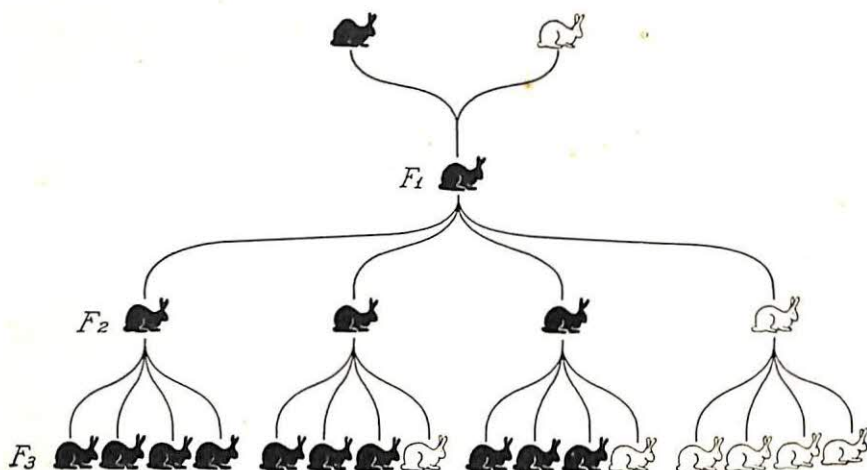


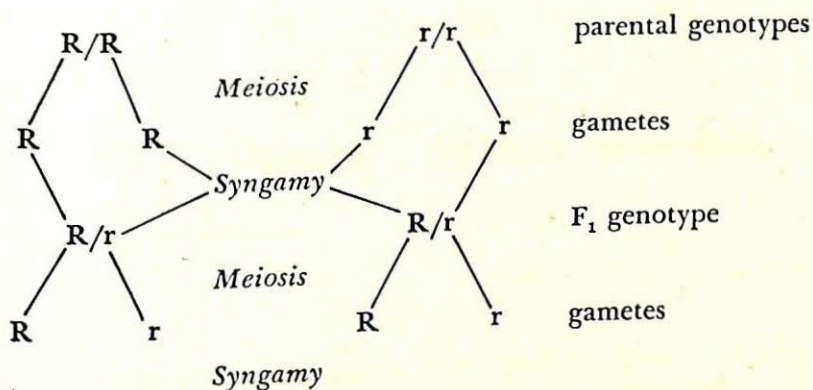
FIG. 17. Cross of a purebred colored rabbit with an albino rabbit. F_1 , first generation, all offspring colored. F_2 , second generation, colored and albino rabbits in the ratio 3 : 1. F_3 , third generation, pure colored, segregating, and pure albino families in the ratio 1 : 2 : 1. (Redrawn from Mohr's *Heredity and Disease*. Courtesy of W. W. Norton & Co.)

they have received from their common ancestry at least some of the same genes, are much more likely to possess common recessives than unrelated people. This appears clearly in the pedigree for albinism shown in Fig. 18 (p. 91). The uncle-niece marriage (*A*), which resulted in four albinos among six children, shows that the uncle must also have carried the albino gene. The first-cousin marriage (*B*) also showed, by the production of an albino child, that the parents carried this gene in common.

With these principles in mind, let us next compare with the crosses involving albinism some similar crosses in which neither of the two alleles is dominant, but in which the phenotype results from their approximately equal effectiveness. And to remind ourselves that the phenomena of meiosis and syngamy are essentially similar in all organisms, let us select an example from a plant—a seed plant.

There are both red- and white-flowered four-o'clocks (*Mirabilis jalapa*). The cross red by red gives only red-flowered offspring; white by white gives only white-flowered plants.

These two types are homozygous. When a red flower is crossed with a white one, all the first generation (F_1) are pink; and if we cross together two pink flowers, we get 1 red : 2 pink : 1 white, in the second generation (F_2). Evidently the genes determining this difference in color are alleles (R and r). When we diagram these crosses, however, they turn out to be just like the albino case.



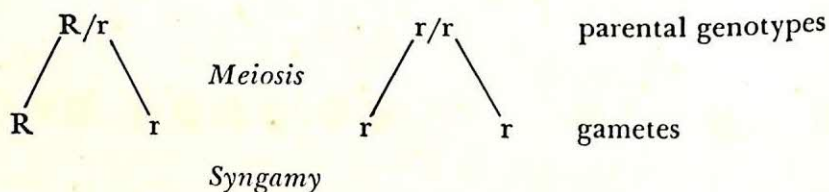
	R	r
R	R/R	R/r
r	R/r	r/r

1 R/R : 2 R/r : 1 r/r

The genotypic ratio is still two heterozygotes to one of each of the homozygotes, as before. The phenotypic ratio is, however, not 3 : 1, but 1 red : 2 pink : 1 white. Thus we learn that the genotypic ratio, which depends solely upon the nature of meiosis and syngamy, is constant for a given type of cross, while the phenotypic ratio depends upon the relative dominance of the alleles and varies with this from case to case. The blending of red and white in the hybrid only serves to emphasize even more strikingly the fundamental independence and aloofness of the alleles. For it is clear that "the genes themselves neither blend nor contaminate one another. When

reduction brings the time for parting, each goes its solitary way, bearing no trace of having been associated for months or years with the other within the microscopic chambers of the cells. Moreover, it evidently makes no difference whether we use a red-flowered plant for our original male parent and a white for our female, or vice versa. In both cases the hybrids will be pink. All that matters is the kind of genes in the resulting mixture." ²⁰

One more example from the four-o'clock, this time a cross between a heterozygote and a pure white:



	r	r
R	R/r	R/r
r	r/r	r/r

Genotypic ratio 1 R/r : 1 r/r

Phenotypic ratio 1 pink : 1 white

This is the same result we obtained for the corresponding cross of heterozygous nonalbino with albino, and as before, the phenotypic ratio indicates precisely the proportions of the types of gametes formed by the heterozygous parent. Such a cross, known as a *backcross*, is for this reason of great practical value, since it enables us to determine the frequencies of the various types of gametes an individual produces. By backcrossing to the homozygous recessive type—in the absence of dominance either homozygote would do—we may discover the hidden genotype which is of such ultimate importance.

²⁰ Wells, H. G., Huxley, J., and Wells, G. P. *The Science of Life*, Chap. I, pp. 479-80. Doubleday, Doran, New York, 1931.

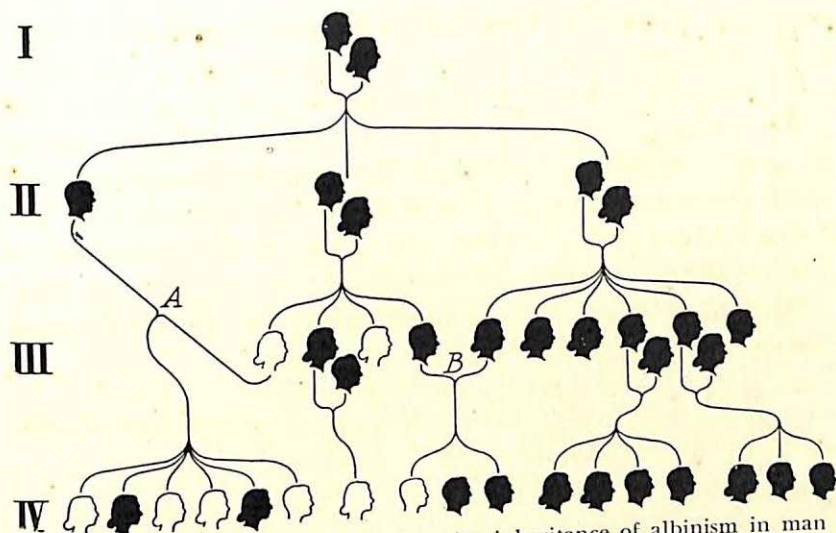


FIG. 18. A pedigree illustrating the recessive inheritance of albinism in man through four generations (I-IV). At *A*, a marriage of a heterozygous uncle with an albinotic niece; a backcross. At *B*, a marriage of heterozygous first cousins. (After Tertsch)

In the Andalusian fowl there is another sort of blending, one which results in a distinctly new type. Black and splashed-white are homozygous, and when crossed blend to produce the highly regarded "Blue Andalusians." Since these are heterozygotes, like the pink four-o'clocks or the heterozygous nonalbinos, when interbred one fourth of their offspring are of one homozygous type (black), and another one fourth are of the other (splashed-white). Imagine the chagrin of the fancy breeder trying to get a line of Andalusian blues that would breed true!

Another common sort of blending involves lethal genes. Dexter cattle are relatively short-legged but otherwise normal. However, they do not breed true but, like the Andalusian blue fowls, show the marks of heterozygosity. Dexter bull crossed by Dexter cow gives one fourth normal, one half Dexter, and one fourth "bulldog" calves. The latter, as described in the last section (Fig. 13), are stillborn or die shortly after birth. The short-leggedness of Dexter cattle is

therefore a blend of the effects of the lethal gene and its normal allele.

Lethals that are completely recessive are very abundant. They can be detected by the change in the expected ratios. If L is the normal allele, and l the lethal, the cross $L/l \times L/l$, instead of producing 3 dominant to 1 recessive, will apparently produce only dominant offspring, as the recessives die off during development. Dominant lethal mutations presumably occur, too, but as they kill every individual carrying them at once, they cannot be inherited.

Earlier we noticed that a gene is not limited to two states (p. 79). While in man only two alleles of the albino gene are known, in mice there are four, in rabbits six, and in guinea pigs five. In *Drosophila* there is one series, affecting eye color, which numbers no less than thirteen alleles that can be distinguished from one another. However, inasmuch as every diploid cell carries its genes in pairs, not more than two members of any such series of *multiple alleles* can be present at one time. The crosses "albino by nonalbino" and "red- by white-flowered four-o'clock" therefore serve equally well as examples for crosses involving multiple alleles. The only additional factor to be taken into account is the dominance of the alleles. This can be discerned at once from the phenotype of the offspring of a cross between homozygotes.

Take, for example, the albino series in rabbits. One allele produces, when homozygous, a form known as the Himalayan albino, which has black extremities—feet, ears, tail, tip of nose (Fig. 19). Cross a homozygous Himalayan albino (c^h/c^h) with a pure full-color (C/C), and the hybrids (C/c^h) are all full-color. The gene for Himalayan albinism is, therefore, recessive to that for full-color. But cross the same Himalayan albino with a full albino (c^a/c^a), and all the offspring (c^h/c^a) are Himalayan albinos. The gene for Himalayan albinism must be dominant to that for complete albinism. The same gene can be both dominant and recessive, depending upon which allele it is compared with. *Dominance is*

purely relative. Still another allele of this series is shown in the illustration. This is chinchilla (c^{ch}), which has no yellow in the fur, and is consequently a silvery gray, highly prized by furriers. Chinchilla is dominant to both Himalayan and albino, but is recessive to full-color, so that the series, in order of dominance, runs as follows: $C > c^{ch} > c^h > c^a$.

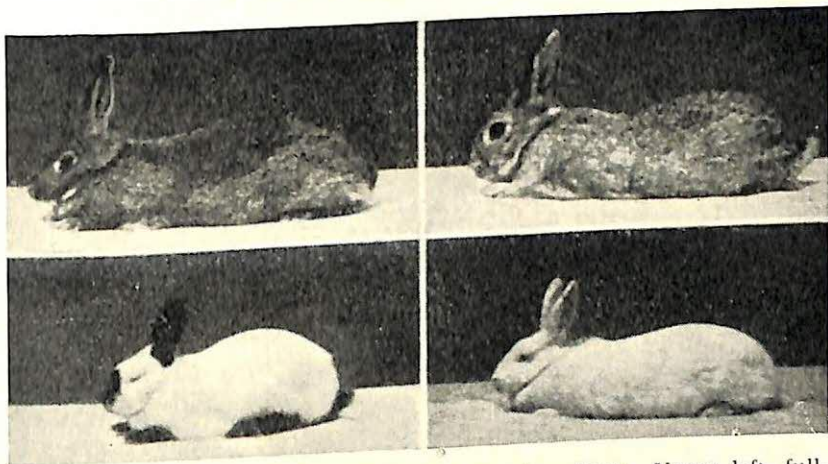


FIG. 19. The albino series of multiple alleles in rabbits. Upper left, full-color; upper right, chinchilla; lower left, Himalayan; lower right, albino. (From Snyder's *The Principles of Heredity*. Courtesy of D. C. Heath and Company)

The relation between any two alleles of such a multiple series could, of course, also lack dominance (perfect blending), or dominance might be incomplete. An interesting combination of several such relationships is to be found in man. The best known multiple allelic series in human beings consists of three members which determine the blood groups. To understand the nature of these we must digress a little.

Foreign proteins (antigens) injected into the circulation of an animal stimulate the cells of the animal to produce characteristic antibodies which will react with their antigens and neutralize their effects. When observed outside the body,

this reaction frequently takes the appearance of a clumping, or agglutination, of the antigen.

In 1900 Dr. Karl Landsteiner, then in Vienna,²¹ discovered that the red blood cells of some people would clump in the blood serum of certain, though not all, other people. Evidently not only do red blood cells act as antigens, but those of some people are the specific antigens for the normally occurring antibodies in the blood of others. There are, in fact, two such antigens in human red blood cells, named A and B, and, correspondingly, there are two antibodies in the serums. Landsteiner and others found that some people had both the antigens, some had either one alone, some had neither. These are the blood groups AB, A, B, and O, respectively.

Of course, if a person carries a particular antigen, he must be lacking in the corresponding antibody; else his blood would agglutinate in the vessels and stop the circulation. It is not so clear why every person who lacks a particular antigen should be provided with the complementary antibody, but this too is the rule. When suspensions of red blood cells are mixed under the microscope with each of several serums known to contain particular antibodies, any person's blood can be quickly typed, for clumping indicates the presence in the cells of the specific antigens for whatever antibodies are known to be present.

The first and most widely known use of this knowledge was to make blood transfusions safe, but the distribution of the blood groups among relatives early attracted investigation, too. Certain parents never had particular blood groups represented among their children. These findings are summarized in Table I.

Very little analysis is needed to see that the O group behaves as a typical recessive. O by O matings always produce only O children, though these may come also from other

²¹ Dr. Landsteiner has long been in America, associated with the Rockefeller Institute. He was awarded the Nobel prize for medicine in 1930.

TABLE I

<i>Blood groups of parents</i>	<i>Blood groups which may occur in children</i>	<i>Blood groups which do not occur in children</i>
O × O	O	A, B, AB
O × A	O, A	B, AB
A × A	O, A	B, AB
O × B	O, B	A, AB
B × B	O, B	A, AB
A × B	O, A, B, AB	—
O × AB	A, B	O, AB
A × AB	A, B, AB	O
B × AB	A, B, AB	O
AB × AB	A, B, AB	O

(From L. H. Snyder, *The Principles of Heredity*, p. 96, D. C. Heath, Boston, 1935)

crosses; while O-type children never occur when one of the parents is of group AB. On the other hand, A by B type parents may have children of group AB, so that here we find blending. All the results can be explained if we assume the blood groups are due to three alleles, A^A and A^B blending, a recessive to both. The first two produce the antigens included in their symbols as superscripts, while a is ineffective in producing either. In the accompanying diagram (Fig. 20) the possible genotypes within each of the four blood groups are given, and the gametes each genotype will produce. By the proper combinations of these gametes for any given mating, the empirical results of Table I can be obtained.

From the table we can also see that neither antigen A nor antigen B ever appears in a child's blood unless it was present in at least one of the parents. This, which is merely a particular instance of the general behavior of dominants, has been used widely in legal medicine to determine parentage.

A few years ago there was a famous "baby case," in which one of two mothers who went home from the hospital at the

same time claimed she had received the wrong baby, a claim the other mother disputed. Sometimes an analysis of the blood groups can instantly clear up any such doubt. In this instance, for example, two of the parents were each of group O, while the baby they had been given was of group A, manifestly not their own. In the other family, the father belonged

The Major Blood Groups

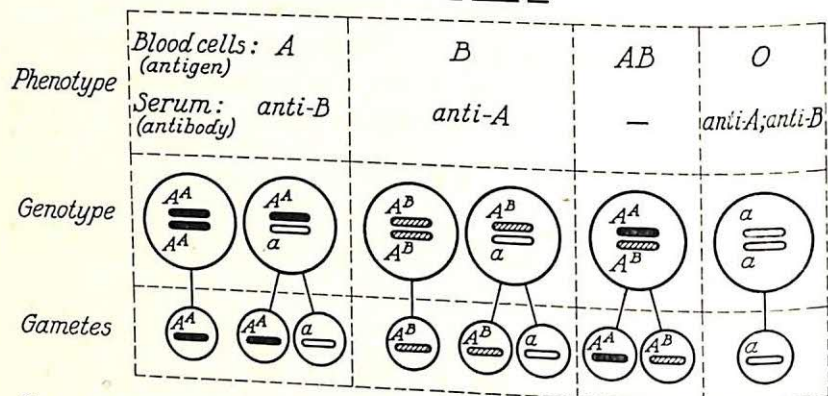


FIG. 20. The major blood groups. A diagram to illustrate the genotypes of the individuals belonging to each of the four major blood groups, and the kinds of gametes they produce respectively. The chromosomes carrying the three alleles, AA , AB , and a are differently shaded.

to group O, the mother to group AB, and their presumed baby was of group O—again an impossibility. But the heritage of the babies would fit very well into the opposite families. It was evident that an error had been made, and the court ordered the babies exchanged. Very frequently, of course, blood tests cannot show anything decisive in these cases, as often either of the disputed sets of parents could have produced either child. Unfortunately this is especially likely to occur in cases where paternity alone is questioned, since blood tests can reveal only whether a particular man could or could not have been the father, and the former indication is several times as likely as the latter.

The blood groups have also been used in studies of racial

relationships, since the proportions of the four groups in the population vary from race to race. It is interesting, too, that these same blood groups occur among the great apes.

Whenever, in such studies, the analysis of the four standard groups remains inconclusive, recourse may be had to another pair of antigens found to be present in human red blood cells, but unaccompanied by normal antibodies. These antigens are called M and N, and depend, respectively, on a single pair of alleles, M and N . As neither of these is dominant over the other, the genotype M/N results in the production of both antigens. In the accompanying diagram are given the phenotypes (blood groups); their respective genotypes; and the types of gametes formed by each (Fig. 21).

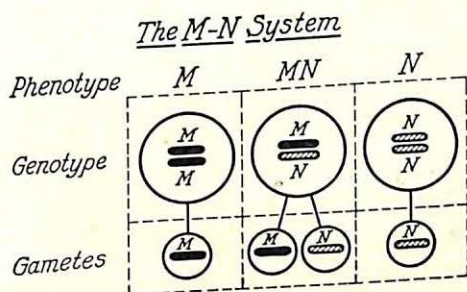


FIG. 21. The minor blood groups, illustrating the genotypes of individuals of each group and the kinds of gametes they produce.

Alleles do not necessarily affect the same trait. In *Drosophila*, for example, there is a gene which in one form produces a disarrangement of the orderly rows of facets in the compound eye of the fly. An allele which produces no discernible effect on the eye causes neat little scalloped incisions at the tips of the wings. The heterozygote is *completely normal*, without either facet disarrangement or notches on the wings. In another allelic series one member, known as *vortex*, causes peculiar volcano-like vortices on the thorax; a second, called *oblique*, lops off the wing-tips; while a third, *dumpy*, does both. The heterozygote between *dumpy* and

vortex has vortices on the thorax but normal wings. Similarly, the dumpy/oblique heterozygote has lopped wings, but a normal thorax. The vortex/oblique heterozygote is perfectly normal, having neither characteristic!

These facts are enough to show us that alleles may interact in a number of possible ways. As a result, dominance and the phenotypic ratio vary from case to case. Were it not for the constancy of the genotypic ratio, based upon the nature of meiosis and syngamy, no order could be discerned in hereditary phenomena!

The inheritance of two or more independent pairs of alleles

Having now seen how a single pair of genes behaves in inheritance, we are prepared to follow *two* independent pairs at once. Since inbreeding of the offspring, necessary for an analysis of the second generation (F_2), is taboo in human society but is permissible in animal-breeding, this time we shall use guinea pigs. If we mate a guinea pig from a breed pure for rough coat and colored fur with one from a breed pure for smooth coat and white (albino) fur, the offspring (F_1) are all rough and colored. Rough (R) and colored (C) are therefore dominant to smooth (r) and white (c^a). The gametes of the first parent all carried R and C , and those of the second r and c^a . Moreover, if independent, these pairs must lie in separate pairs of chromosomes, as in Fig. 22.

Non-homologous chromosomes, as we have learned, assort at random during meiosis. In the doubly heterozygous F_1 offspring, this results in four kinds of gametes, one for each of the four possible combinations of the genes. Two of these are the original combination, $R;C$ and $r;c^a$, while the other two, $R;c^a$ and $r;C$,²² are new. These occur in both eggs and sperm, so that at syngamy 4×4 or 16 combinations result (Fig. 23). Adding these classes, we get 9 rough, colored ■;

²² Symbols for genes located in different chromosomes are separated by a semicolon.

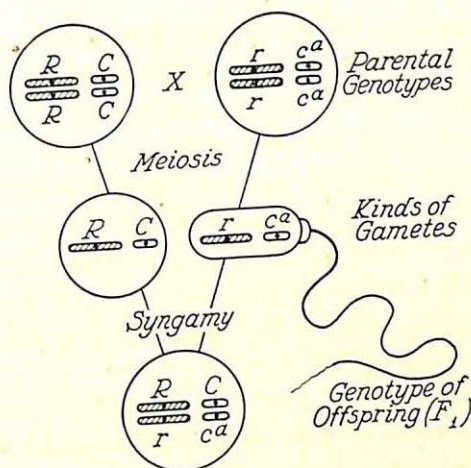


FIG. 22. Results of crossing two purebred strains of guinea pigs differing in two pairs of independently assorting characteristics. *R*, rough coat, dominant; *r*, smooth coat, recessive. *C*, colored coat, dominant; *ca*, albino, recessive.

3 rough, white □; 3 smooth, colored ●; and 1 smooth, white ○. This phenotypic ratio was first discovered by Mendel in peas. For example, peas with round yellow seeds crossed with those having wrinkled green seeds produced only round yellow

		<u>Eggs</u>			
		<i>R; C</i>	<i>R; ca</i>	<i>r; C</i>	<i>r; ca</i>
<u>Sperms</u>	<i>R; C</i>	$\frac{R}{R}; \frac{C}{C}$ ■	$\frac{R}{R}; \frac{ca}{C}$ ■	$\frac{r}{R}; \frac{C}{C}$ ■	$\frac{r}{R}; \frac{ca}{C}$ ■
	<i>R; ca</i>	$\frac{R}{R}; \frac{C}{ca}$ ■	$\frac{R}{R}; \frac{ca}{ca}$ □	$\frac{r}{R}; \frac{C}{ca}$ ■	$\frac{r}{R}; \frac{ca}{ca}$ □
	<i>r; C</i>	$\frac{R}{r}; \frac{C}{C}$ ■	$\frac{R}{r}; \frac{ca}{C}$ ■	$\frac{r}{r}; \frac{C}{C}$ ●	$\frac{r}{r}; \frac{ca}{C}$ ●
	<i>r; ca</i>	$\frac{R}{r}; \frac{C}{ca}$ ■	$\frac{R}{r}; \frac{ca}{ca}$ □	$\frac{r}{r}; \frac{C}{ca}$ ●	$\frac{r}{r}; \frac{ca}{ca}$ ○

Genotypes and Phenotypes of Offspring

FIG. 23. Recombination in the second generation, after a cross between two purebred strains differing in two pairs of independently assorting characteristics. See Fig. 22. Phenotypes, ■ rough, colored; □ rough, white; ● smooth, colored; ○ smooth, white. Arrows indicate similar genotypes.

seeds in F_1 , and in F_2 produced 315 round yellow, 101 wrinkled yellow, 108 round green, and 32 wrinkled green seeds. This is a very close approximation to the expected 9 : 3 : 3 : 1 ratio.

The *genotypes* are nine in number, in the following ratio (corresponding genotypes are connected by arrows in Fig. 23): 1 $R/R;C/C$: 2 $R/r;C/C$: 2 $R/R;C/c^a$: 1 $R/R;c^a/c^a$: 4 $R/r;C/c^a$: 1 $r/r;C/C$: 2 $R/r;c^a/c^a$: 2 $r/r;C/c^a$: 1 $r/r;c^a/c^a$. Hence there are four genotypes among the doubly dominant individuals, two among each of the singly dominant groups, and only in the case of the doubly recessive group can one be sure of homogeneity. Inasmuch as each genotype behaves differently in breeding, any attempt to breed merely according to the phenotypical classification is almost certain to go astray.

How can the breeder, then, find out the genotype? The backcross to the doubly recessive type will reveal it, for then, just as in the crosses with a single pair of factors, the offspring will have phenotypes which correspond to the gametes of the animal or plant tested. If, for instance, we cross a rough, colored hybrid guinea pig ($R/r;C/c^a$), which produces the four types of gametes found in Fig. 23, with a smooth, white mate—which, being homozygous, forms only one sort of gamete—we obtain the result shown in Fig. 24. Four kinds of offspring, corresponding to the four kinds of gametes formed by the hybrid, occur with equal frequency. A cross to a type recessive for all the pairs of genes being followed is therefore a *test-cross*, which enables us to determine the genotype of any individual.

To go further and show how three independent pairs of factors behave in inheritance would only be laborious and would involve no new principle. The Mendelian principle of the independent assortment of gene pairs, just illustrated, may be formulated in a simple mathematical way and extended to any number of independent pairs of genes.

The formula 2^n gives the number of gametic combinations for any number of independent pairs of genes on the basis

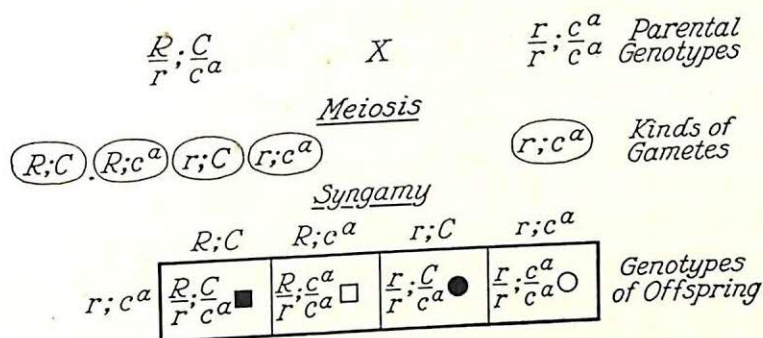


FIG. 24. Results of crossing a hybrid for two pairs of characteristics with a mate homozygous for both recessive traits; the test-cross. Phenotypic ratio is 1 rough, colored : 1 rough, white : 1 smooth, colored : 1 smooth, white.

of chance, just as for chromosomes (see p. 68). Gametes also unite by chance, and each individual is therefore the combination of two gametes whose individual genotypes each have a probability of $\frac{1}{2}^n$. What is the chance for the union of any two particular combinations? This is given by a well-known law of probability which states that the chance of coincidence of two or more independent events is the product of the probabilities of each of the events. For example, the chance that any penny will fall heads is $\frac{1}{2}$. The chance that two pennies flipped together will both fall heads is therefore $\frac{1}{2} \times \frac{1}{2} = \frac{1}{4}$, the product of the probabilities that either alone will fall heads. Applying this principle to any number of pairs of genes:

<p>2 pairs</p> $2^n \times 2^n$ $2^2 \times 2^2 = 16$	<p>3 pairs</p> $2^n \times 2^n$ $2^3 \times 2^3 = 64$
---	---

These expressions may be factored:

$$(2 \times 2) (2 \times 2) = 16 \quad \text{and} \quad (2 \times 2) (2 \times 2) (2 \times 2) = 64.$$

When one allele is dominant and the other is recessive, the phenotypic ratio for the F_2 , we found, is 3 dominant to 1

recessive (3:1). We may substitute this ratio for its equivalent expression (2×2) in the equations, since both represent the product of the gametic combinations:

$$(3:1)(3:1) = 16 \quad \text{and} \quad (3:1)(3:1)(3:1) = 64.$$

Multiplying out, we then get the phenotypic ratios:

$$9:3:3:1 = 16 \quad \text{and} \quad 27:9:9:9:3:3:3:1 = 64.$$

The largest class is that displaying all dominant traits, next largest are those displaying one less dominant, and so to the smallest class, which will have no dominant genes.²³ The application of the formula will readily yield the phenotypic ratio for any number of independent pairs of alleles, each yielding a 3:1 ratio alone.

If two particular alleles blend instead of exhibiting clear dominance and recessiveness, the phenotypic ratio for such a case (1:2:1) is simply substituted for 3:1. The consequences can thus be calculated for any number of pairs of genes in any combination of allelic relations, simply by algebraic multiplication.

Here, as in the arrangement of the chromosomes on the meiotic spindle, *chance* prevails. Here, once again, there is an exact parallel between the behavior of genes and chromosomes. The pairs of chromosomes assort at random—so do the independent pairs of genes we have been considering.

This has been a long section. It will be well to pause and review what we have learned of heredity thus far:

1. Heredity is due to units (genes) which, because of syngamy, are paired (alleles) in individuals.
2. The process of meiosis results in the segregation of alleles.

²³ It is worth noting that the first number of such a phenotypic ratio gives the number of different genotypes present. Thus there are, respectively, 9 and 27 genotypes in the two crosses illustrated here.

3. Syngamy of a particular sperm and egg is a product of chance and, hence, brings about a random recombination of alleles from the two parents.
4. While present in the same cell, alleles interact to affect traits in a variety of ways (complete dominance of one, incomplete dominance, equal blending; alleles do not even always affect the same trait).
5. The genes themselves are unaltered by their interaction.
6. Gene pairs which are inherited independently show random assortment at meiosis.

Though not expressed in his terms, these are the principles Mendel discovered. Only the further observation of the parallel behavior of genes and chromosomes came later, opening new avenues of interpretation, which we are now ready to explore.

GENE LINKAGE AND CROSSING OVER OPPOSE EACH OTHER IN
THEIR EFFECT UPON VARIETY AMONG INDIVIDUALS

Mendel's discoveries of the unitary nature of the hereditary material and of the role of chance in providing recombinations of the units in gametes and zygotes were made during the very period when Oskar Hertwig and Strasburger were led to assert that the chromosomes must be the carriers of heredity. Yet neither the demonstrations of the persistent individuality of the chromosomes nor the unique manner in which they are duplicated and distributed in equivalent sets to each new cell, through the mechanism of mitosis, furnished final proofs of the "Chromosome Theory of Heredity." The rediscovery of Mendel's work brought out at once the striking series of parallels between the deduced behavior of the hereditary factors and the transmission of the chromosomes in meiosis and syngamy. It was seen that in gametes the chromosomes are unpaired (haploid)—while, to account for the facts, so must be the alleles. In the zygote, and in all its descendant somatic and prospective germinal cells, the chromosomes are

paired again (diploid), with a maternal chromosome corresponding to each paternal chromosome—and so are the alleles. At meiosis homologous chromosomes disjoin—and so do alleles. Different pairs of chromosomes assort at random—and so do the pairs of genes we have considered.

All these facts serve to strengthen our belief in the theory, yet none of them are conclusive. It is really to the exceptions to typical "Mendelian" inheritance that we must turn for the most convincing evidence that in the chromosomes, whose nature we can study and whose behavior we can to some extent learn to control, lie the genes, marking the ultimate goal in our quest for an understanding of life.

As the first exception, we learn that Mendel's principle of the independent assortment of gene pairs is *not always* applicable. The number of genes is much larger than that of their chromosome-carriers; hence a number of genes must lie in each of the chromosomes. Consequently, genes in the same chromosome cannot be transmitted independently in cell division; they are linked. Moreover, since at meiosis each chromosome has a partner from which it disjoins, the genes in any one chromosome and their alleles in its homologue are not transmitted independently either. Together they form one "linkage group." Only gene pairs in different pairs of chromosomes can assort independently.²⁴ *Consequently the number of linkage groups corresponds to the number of chromosome pairs.*²⁵

²⁴ Mendel found independent assortment of *all seven* of the pairs of alleles he studied in the pea. This was an amazing chance, for there are only *seven* pairs of chromosomes in the pea! But for a qualification of this generalization, see pp. 116-117.

²⁵ This relation was first predicted by W. S. Sutton, while a graduate student at Columbia University, in 1903. In his thesis for the Ph. D. degree, he proposed the theory that the paired Mendelian factors lie in paired chromosomes, such as he had been studying with Montgomery in lubber grasshoppers. He also pointed out that the independent assortment of different pairs of genes is due to the chance position of the maternal and paternal chromosomes of different pairs upon the spindle at the reduction division. The meteoric rise of genetics as a science has been little more than the proving of these three postulates. Sutton, however, choosing medi-

The first case of linkage turned up in the sweet pea (*Lathyrus*), in 1906. A cross involving two pairs of genes showed that the gene for purple flowers and the gene for cylindrical pollen grains were inherited together, and, conversely, those for red flowers and disk-shaped pollen. Every form of plant and animal subjected to breeding since that time has, when sufficiently analyzed, yielded additional instances.

An exact correspondence between the number of linkage groups and the number of chromosome pairs has not always been found, mainly because of the great labor involved in determining it, especially when the haploid chromosome number is high. But in those organisms which have been studied intensively and which have a low chromosome number, such as Indian corn, sweet pea, and some six species of *Drosophila*, there is perfect correspondence. In *Drosophila melanogaster* several thousand genes have been tested, and each falls into some one of four linkage groups corresponding to the four pairs of chromosomes (i. e., the haploid number).²⁶ The suc-

cine as a profession, had no further part in the advance of the science he played so large a part in founding.

²⁶ There is one mechanism, however, which may reduce the number of linkage groups below the haploid chromosome number. In Chap. I (p. 17), we learned that x-rays often break chromosomes, and that fragments may become reattached elsewhere. Thus pieces may be interchanged between chromosomes of different pairs, a situation known as a "translocation." Since pairing is ultimately a property of genes, each compound chromosome resulting from translocation will have, at meiosis, more than one partner with which to pair and from which to separate. The contrast between normal pairing and that when a translocation is present will be clear from the diagram below (Fig. 25). The two original pairs of chromosomes are differently shaded.

Now this situation will affect the linkage of the genes. Suppose one pair of genes, A/a , to be located on one of the original pairs of chromosomes (unshaded), and another pair of genes, B/b , to be on the other (shaded). Different pairs of chromosomes assort independently. We can then expect random assortment for A/a and B/b . But when a

translocation has involved two of the chromosomes of these pairs, two of these hitherto independently assorting genes— a and B , for example—will now lie in

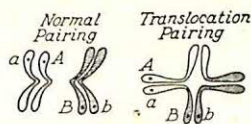


FIG. 25

cessful confirmation of our prediction that the genes will be inherited in linkage groups if they are located in the chromosomes serves as further evidence to convince us that our theory is correct.

Now what alteration does the existence of linkage make in the pattern of heredity? We have seen that the number of possible combinations which can be made up by taking at random one member from each pair of units is 2^n , where n is the number of such pairs. In meiosis n is the haploid chromosome number. Then 2^n is well up in the millions for mankind, but in any organism which has a low haploid number or in which translocations reduce the number of linkage groups to the equivalent of a low haploid number, it is rather small. In *Drosophila*, for instance, 2^n is only 16. Wherever the genes within each chromosome are inseparable, the maximum number of variant offspring from a cross between two individuals which have no two homologous chromosomes exactly alike in any of the linkage groups is then $(2^n)^2$. It would amount, for *Drosophila*, to only 256. On the other hand, if the individual gene pairs were able to assort at random, 2^n would amount approximately to 2^{3000} , and this num-

the same compound chromosome. They will therefore be inherited together! That will be true for all the genes in this compound chromosome, although they were originally of different linkage groups; and, of course, those in the other compound chromosome will be inherited together, too. Moreover, since none of these four chromosomes can now assort independently of the others, all the genes of the two original linkage groups will form one interdependent group. A translocation changes two linkage groups into one.

Translocations, like gene mutations, occur spontaneously as well as through the action of x-rays. Since they may involve interchanges between more than two pairs of chromosomes, we may have larger groups of partially pairing chromosomes, six, eight, or more. Correspondingly, three, four, or more linkage groups may become combined into one. This is especially common in certain species, like the evening primrose (*Oenothera*) and the Jimson weed (*Datura*); it is the most probable reason why in some forms, such as the grouse locust (*Apotettix*) and the West Indian guppy (*Lebistes*), which have numerous chromosomes, all the genes nevertheless appear to be inherited in a single linkage group. This situation is after all not very common, and we are not likely to meet with it in any of the organisms in which we are most interested. Its main import is evolutionary.

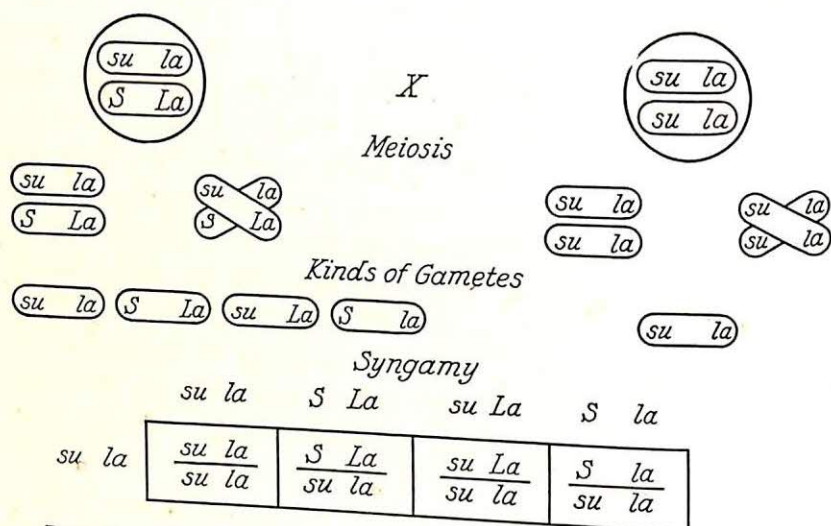
ber squared would be utterly inconceivable. Thus a *limit is set to variation by the linkage of the genes. The fewer the linkage groups, the more rigid will be the restriction on the number of combinations.*

Actually, there is much more variation than this would lead us to expect. The fruit fly, for instance, is certainly not limited to 256 gene combinations per couple. How is this? If linkage were complete, two pairs of genes A/a and B/b belonging to the same linkage group (with A and B together in one chromosome and a and b together in its homologue) would always segregate in the combinations AB and ab . Yet even in the first observed case of linkage, that in the sweet pea mentioned at the beginning of this section, it was observed that these original combinations were often broken up, and recombinations (Ab and aB) appeared. Evidently genes in the same chromosome may part company and come to lie in homologues. In fact, this capacity is quite general, for every organism in which linkage has been studied has revealed this sort of recombination. Yet linkage is not nullified by it, as we shall see.

Suppose we take an example from maize. A certain recessive gene (su) produces sugary endosperm in the kernels, making sweet corn fit for our tables rather than the starchy field corn we feed to livestock. It is linked to another recessive gene called *lazy* (la), which produces such a weakening of the stalks that the plants straggle and lie prone on the earth. By crossing a plant heterozygous for these two genes ($\frac{su}{S} \frac{la}{La}$) with a homozygous recessive ($\frac{su}{su} \frac{la}{la}$), we can test the former for the kind of gametes it produces (as shown in Fig. 26).

All four possible types are present in the offspring of our cross, both the two original combinations and two recombinations. In looking over the offspring we would, no doubt, notice that the recombinations were much scarcer than the original combinations. In a large number, which should

be counted to get an accurate measure of the ratio, there would turn out to be approximately 45.5 per cent of the sugary lazy plants, a like amount of the Starchy non-lazy, 4.5 per cent of the Starchy lazy, and a like amount of sugary non-lazy. The total recombination for these gene pairs is therefore 9.0 per cent.



*Result: Original combinations: sugary lazy; Starchy non-lazy.
Recombinations: sugary non-lazy; Starchy lazy.*

FIG. 26. Recombination between the linked characters sugary endosperm (*su*) and lazy stalks (*la*) in maize, as shown in a test-cross. In the progeny all possible combinations of the characters and their opposites occur in equal proportions, regardless of whether the combinations are the original ones (sugary lazy; Starchy non-lazy) or are recombinations (sugary non-lazy; Starchy lazy). But the original combinations and the recombinations are not equally frequent.

Now we know that all the observed recombinations must have taken place in the heterozygous parent.²⁷ The phenotypes of the offspring, therefore, reflect the genotypes of the gametes, both the original kinds and the recombinations.

²⁷ It is obvious, from Fig. 26, that there can be no recombination in a homozygous individual. Even when one of two pairs of genes is heterozygous, all gametes formed must still be identical; *AB/aB* can produce only *AB* and *aB* gametes.

which are produced by this parent. We can go a step further. Since one parent furnishes only a single sort of gamete (100 per cent *su la*), the various *frequencies* of the phenotypical classes must correspond to the different frequencies of the types of gametes supplied by the other—the heterozygous—parent. There must then have been 45.5 per cent *su la* gametes; 45.5 per cent *S La*; 4.5 per cent *su La*; and 4.5 per cent *S la*. This is a particular instance of the more general fact that the frequency of any class is the numerical *product* of the frequencies of the gametes uniting to form it.

To sum up, the test-cross has made apparent, in the phenotypes of the offspring, the gene combinations and their frequencies among the gametes of the tested parent. Of all crosses, this to the homozygous recessive is the most revealing and most valuable to the geneticist and breeder.

Now, how can recombination take place if the genes concerned actually lie in the same chromosome? How do alleles change places? Observations in both Indian corn and fruit fly have demonstrated the general nature of the mechanism. In *Drosophila*, Curt Stern²⁸ was able to obtain homologous chromosomes which were visibly different. By the translocation process described a little while ago, one chromosome had been broken in two,²⁹ while the other had a long piece attached to it. Known to lie in one of the short pieces were two mutant genes, a recessive producing carnation-colored eyes (symbol *car*), and a dominant narrowing the eyes (Bar—

²⁸ Curt Stern, now at the University of Rochester, is a refugee from Nazi Germany. His monographs in German on *Advances in the Chromosome Theory of Heredity, Linkage and Crossing Over*, and *Multiple Allelism* are indispensable to the geneticist:

"Fortschritte der Chromosomentheorie der Vererbung." *Ergebnisse der Biologie*, Vol. 4, pp. 206-359, 1928.

Faktorenkoppelung und Faktorenaustausch. "Handbuch der Vererbungswissenschaft," No. 19. Gebrüder Borntraeger, Berlin, 1933.

Multiple Allelie. "Handbuch der Vererbungswissenschaft," No. 14, Gebrüder Borntraeger, Berlin, 1930.

²⁹ Both pieces of this broken chromosome segregate normally, as one has its original spindle attachment and the other is preserved from being lost by translocation to another chromosome (not shown in Fig. 26).

symbol *B*). In the homologous chromosome, with the extra limb were the normal alleles of these two genes. (*A* + superscript is the symbol for any normal allele.) The pair of chromosomes may, therefore, be diagrammed in the following way (Fig. 27).

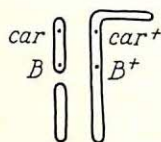


FIG. 27. The two modified sex chromosomes of *Drosophila melanogaster* used in the cytological demonstration of crossing over. The broken chromosome carried the mutant genes for carnation eye color and for Bar eye; the chromosome with an appendage bore the dominant allele for red eye color and the recessive allele for non-Bar eye. (Stern)

Females of this type and heterozygous for both gene pairs were tested by being crossed to carnation non-Bar males. As expected, the alleles reappeared mainly in the original combinations; but recombinations (carnation non-Bar, and Bar non-carnation) were also present among the progeny. When their chromosomes were examined, every one of the female offspring carrying the original combinations had one of the original kinds of chromosomes present in the mother, along with an unbroken normal homologue from the father. The carnation Bar-eyed ones had the broken chromosome; the non-carnation non-Bar had the chromosome with the extra limb. But, on the other hand, *those showing recombinations of the genes had new kinds of chromosomes*. The carnation non-Bar daughters had two unbroken chromosomes, and the Bar non-carnation daughters had a broken chromosome with an extra limb (Fig. 28). In every single case, recombination of the gene had been accompanied by a chromosomal change!

These types of chromosomes were just what Stern had predicted would arise if the chromosomes actually interchanged at some point between the two pairs of genes, as shown in Fig. 29.

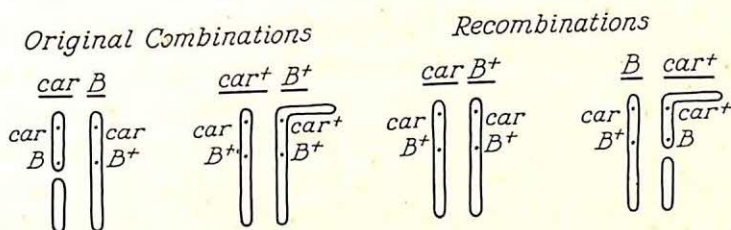


FIG. 28. The test-cross offspring of females of the genotype in Fig. 27, showing how recombination of the genetic characters was accompanied by change in the chromosomes. (Stern)

When might this process, known as *crossing over*, occur? It had long been known that the prophase of the first meiotic division is greatly extended. During this time the homologous chromosomes are at first intimately paired. Later, while still twisted about one another, they loosen up, so as to form a number of internodes and nodes. (The nodes where the chromosomes cross are known as *chiasmata*.) Each node is believed to indicate that the homologous chromosomes have broken and have exchanged equivalent segments during the period when they were intimately paired (Fig. 29).

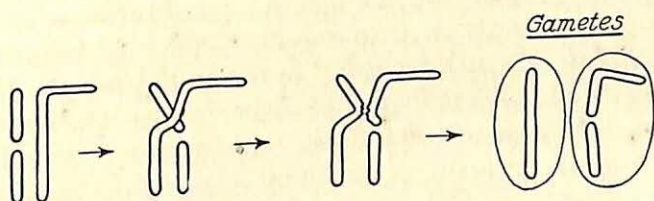


FIG. 29. The mechanism of crossing over: fracture of homologous chromosomes at identical levels and exchange of equivalent segments.

Genes which lie in the same chromosome, then, do recombine, and this recombination is brought about by an exchange of segments between homologous chromosomes. We need go no further to establish our generalization that the limitation of gene combinations which linkage brings about can be counteracted by the possibilities of recombination through crossing over. But to what extent does this recom-

bination actually occur? Can it really nullify the effect of linkage? In exploring these questions, we shall incidentally get a glimpse into the methods which enable the geneticist to say with confidence: "Here is a map of the invisible genes. This is their order and arrangement within each chromosome. Each known gene is here traced to its submicroscopic locus." The human mind has penetrated the secrets of life in no more revealing way.

When a chiasma is formed, the homologous chromosomes have exchanged *segments*, as we have seen (Fig. 29). If, then, the chromosomes carry a great many genes, such segments must assuredly carry more than one gene apiece. Crossing over consequently should result in the recombination, not of single genes, but of whole blocks of genes. In our example we have failed to detect this because only two gene pairs were heterozygous. Had we had several such heterozygous pairs, we could have found out more about the nature of crossing over.

This suggests that we next determine the frequency of crossing over between a number of genes in the same chromosome. Our results will now include various frequencies, although for any two particular genes, under the same conditions, the value appears to be constant. *A* and *B*, for example, cross over 4 per cent of the time, while *A* and *C* cross over 10 per cent of the time. What does this signify?

A. H. Sturtevant,³⁰ in 1913, realized that if the genes are in a linear series, then the farther apart any two genes lie, the higher the chance of a crossover between them. This would account for the different frequencies of crossing over between different genes. How can the hypothesis be tested? If the assumptions we have made are sound, it should be possible.

³⁰ The early development of *Drosophila* genetics was due largely to Thomas Hunt Morgan and three of his students: Alfred H. Sturtevant, Calvin B. Bridges, and Hermann J. Muller. Sturtevant and Muller laid the foundation for our understanding of crossing over, while Bridges, among other things, pioneered in mapping the chromosomes.

by determining crossing-over frequencies, to fix the order of the genes, and to estimate relative distances between them; otherwise not. For example, *A*, we have supposed, crosses over with *B* 4 per cent of the time, with *C* 10 per cent of the time. Let *B* lie four units from *A*, and *C* ten units from *A*. How far is *B* from *C*? A little analysis shows us that, if the linked genes are in a line, it will depend on whether *B* and *C* are on the same side of *A*, or on opposite sides:

$$\begin{array}{c} A \quad 4 \quad B \qquad \qquad C \\ \xleftarrow{\quad 10 \quad} \xrightarrow{\quad} \end{array} \quad \text{or} \quad \begin{array}{c} B \quad 4 \quad A \qquad \qquad 10 \qquad \qquad C \\ \xrightarrow{\quad} \xleftarrow{\quad} \end{array}$$

BC should be either $AC - AB$ or $AC + AB$. In the first case, *B* and *C* would cross over 6 per cent of the time; in the second, 14 per cent. It is a simple matter to determine, by test-cross, which is true. Usually the whole matter can be settled at once by testing an individual heterozygous for each of the three genes. (This is known as a three-point cross.)

Here is an example from *Drosophila*, in which more chromosome mapping has been done than in all other organisms together. Individuals carrying a mutant which reduces the wings to mere stubs (vestigial) were crossed with black-bodied, purple-eyed mates (two mutants).³¹ (It had already been determined that these genes all belong to the same linkage group.) Female offspring,³² all normal-looking, since each of these genes is recessive, were then test-crossed, that is, were mated with black-bodied, purple-eyed, vestigial-winged homozygous males. Their offspring, the F_2 generation, were mostly either vestigial-winged (868) or black-bodied, purple-eyed (843) flies. These were non-crossovers. But *every other*

³¹ To save endless repetition of normal phenotypes, we commonly describe each type only by its *mutant* characters. Thus, the vestigial-winged female fly, it is to be understood, has red eyes and gray body color, while her black-bodied, purple-eyed mates have wings of normal length.

³² Females must be used for testing crossing over in *Drosophila* because there is ordinarily no crossing over in males.

possible combination of these three traits was also represented. In a total of 2,012 flies:

- | | | |
|---|---|--|
| (1) 104 were either black, vestigial; or purple | } | these were recombinations of black and vestigial; and of black and purple. |
| (2) 186 were either black, purple, vestigial; or normal | | these were recombinations of black and vestigial; and of purple and vestigial. |
| (3) 11 were either black; or purple, vestigial | } | these were recombinations of black and purple; and of purple and vestigial. |
| | | |

If we put any three genes in a row, there can be only two intervening regions (1 and 2) in which crossing over might occur (Fig. 30). Where, then, does the third pair of complementary classes come from? Have the chromosomes perhaps

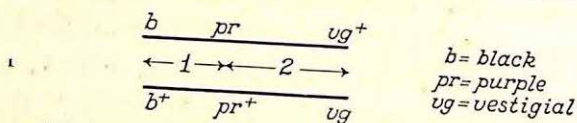


FIG. 30. The regions (1, 2) in which crossing over may be detected when a pair of chromosomes carries three mutant genes at different loci. b , black body color; pr , purple eye color; vg , vestigial wings; b^+ , pr^+ , vg^+ , respective normal alleles in *Drosophila melanogaster*.

crossed over in both regions simultaneously? If the chance of any such "double crossing over" is random, it would be the product of the frequencies of crossing over in each of the regions; and one complementary pair of recombinations ought then to be much scarcer than the others. When we calculate the percentages of recombination³³ between each two genes, we get 5.8 per cent for black and purple, 9.8 per cent for purple and vestigial, and 14.4 per cent for black and vestigial. This indicates that black and vestigial are farthest apart, and

³³ The percentage of recombination for any two genes is simply:

$$\frac{\text{number of individuals showing recombination}}{\text{total number of individuals}}.$$

that purple is in the middle. Then, checking to see whether the complementary classes lowest in frequency equal the product of the major classes, we find: 5.8 per cent of 9.8 per cent = 0.6 per cent; and $11/2012 = 0.6$ per cent. Our hypothesis seems to be right.

We can, then, represent the relations of the three genes, the varieties of crossing over, and the gametes formed, as in Fig. 31.

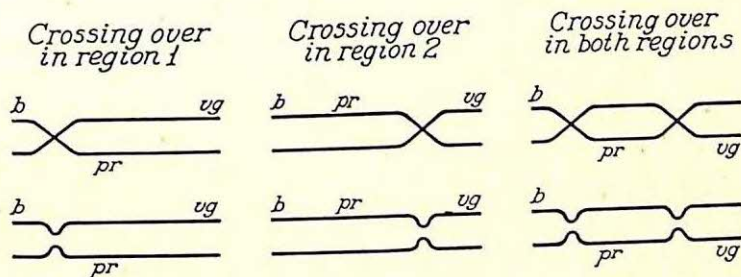


FIG. 31. Diagram illustrating crossing over by regions, in a fruit fly of the genotype shown in Fig. 30. For simplicity, labeling of the normal alleles of the three mutant genes is omitted.

In calculating how often black and vestigial cross over, we must count each *double* crossover between them *twice*. Yet these double crossovers did *not* result in any recombination of black and vestigial.³⁴ Hence, we must add *twice* the frequency of the double crossovers to the 14.4 per cent of recombinations of black and vestigial, $2 \times 0.6 = 1.2$; and $14.4 + 1.2 = 15.6$. This value amounts exactly to the sum of the crossing over in the regions between black and purple and between purple and vestigial ($5.8 + 9.8 = 15.6$ per cent).

³⁴ Every crossover between black and purple recombines these genes; and so, too, for purple and vestigial. But every crossover between black and vestigial does not recombine these two genes, since, in any region as long as this, double crossing over may occur. In shorter regions one crossover prevents any other close to it. This is the phenomenon of *interference*. Because of these double crossovers, the recombination of black and vestigial (14.4 per cent) must always be less than the sum of the recombinations of black and purple (5.8 per cent) and of purple and vestigial (9.8 per cent). This explains why *recombination, for relatively distant genes, is always less than the amount of crossing over between them.*

This is possible only if *the genes are arranged in a linear series.*

It would be rash to say that the percentages of crossing over give us any exact measure of the relative lengths of the intervals between genes, as many factors (x-rays, temperature, age, sex, proximity to end of chromosome or spindle attachment, for instance) can radically alter the frequency of crossing over. But they do serve to indicate approximate distances and to define the serial order of the genes. We may, then, map them in order on a scale, each unit of which represents 1 per cent of crossing over.

This is a sample of the method by which a geneticist maps chromosomes, a preliminary task essential to the analysis of still finer details, the quirks and crotchets of the hereditary pattern. Often enough, these may lead to important discoveries—but we must leave them out of our discussion, if somewhat regretfully, and turn our attention to other aspects of more immediate significance.

What, for instance, is the probability that recombination will occur? How extensive is the variety, among the individuals of a progeny or a population, that can be brought about by crossing over? At one extreme we can find genes which lie in the same chromosome but are so far apart that they will cross over 50 per cent of the time, or more. As 50 per cent recombination amounts to random assortment, which holds for genes in different pairs of chromosomes, this is normally the maximum recombination value.³⁵ Genes as far apart as this behave as though located in different chromosomes. Indeed, their membership in the same linkage group can be detected only when they are tested with some intermediate gene, with which each crosses over less than 50% of the time.³⁶

³⁵ Two genes may cross over more than 50 per cent of the time, but they cannot recombine more often than this, since multiple crossing over then tends to replace them together as often as they are separated.

³⁶ If *B* crosses over 30 per cent of the time with *A*, and 45 per cent with *C*, both *A* and *C* will show linkage with *B*. Yet *A* and *C*, 75 crossing-over units apart, will assort at random. This will account for the occasional instances in which there appear to be more linkage groups than pairs of chromosomes.

The length of a chromosome in this way becomes a crucial factor in controlling the total amount of recombination among linked genes. If, for example, a chromosome is 100 crossing-over units in length, the average gene in that chromosome will assort at random with 25 per cent of the genes in its own linkage group; while, if the chromosome is as much as 200 units long, the average amount of random recombination between its genes will rise to more than 50 per cent! This is no mere theoretical digression—chromosomes frequently attain such lengths! Two of the four kinds of chromosomes in *Drosophila melanogaster* attain 100 crossing-over units in length; in a relative, *Drosophila virilis*, with six kinds of chromosomes, there are two of more than 200 units each, two are about 175 units in length, one is about 125 units, and only one is short. In Indian corn three of the ten chromosomes are more than 100 units, and three more reach 75 units, or more, in length. The number of possible chromosomal combinations in the gametes (2^n) is only 16, 64, and 1,024, in these three organisms, respectively. But so great are the lengths of the chromosomes that the number of elements assorting at random is rendered greater than the haploid chromosome number. This amounts to increasing the exponent in our formula, and is enormously effective in raising the number of possible combinations.

From this first extreme of random assortment between distant genes belonging to the same linkage group, we pass through a middle terrain where recombination is of varying amount, from 50 per cent down. Here the contribution to the total amount of recombination grows less and less. Nevertheless, the very possibility of such recombination, though ever so slight, is an important thing, for it means that *every theoretical genic combination is ultimately possible*. Besides, whenever a particular combination of genes within a single linkage group is but rarely formed, it will, once formed, be all the more likely to stick together, since both combination

and recombination depend on the same frequency of crossing over.

At the other extreme of linkage, we find those genes which cross over only once in a thousand or ten thousand times. Even these, when they do cross over, can, like others which recombine oftener, ultimately enter into any genic combination. Suppose, however, that two genes never cross over, or that they do so rarely enough to escape observation—what then? We must admit that we have no way, at least for the present, to distinguish them as separate genes at all. We cannot see separate genes with our present techniques, nor can we be sure that even the many individual bands of the flies' salivary gland chromosomes correspond to single genes. We cannot define a gene by mutation, for that, as we have seen (p. 79), is a mixed category and is itself defined by the gene. We cannot define a gene by its phenotypic effects, for one gene may have many or few or even none that are apparent. We cannot define it by Mendelian behavior, for that, as we have seen (pp. 103 f.), depends on the nature of meiosis and syngamy, and the units of those processes are not genes, but chromosomes. What do we mean by a gene? There is as yet no practicable working definition but this: *A gene is a single member of the linear series of hereditary factors within each chromosome. Its unitary nature is defined by its separability from its neighbors through crossing over.* The gene has meaning only in the light of linkage and crossing over. These two phenomena, acting in opposition, regulate the amount of reassortment of the genes. Their relative strength in any species helps to determine whether there will be great diversity or marked uniformity among the individuals within any population.

The mechanism of crossing over throws light on yet another process we have discussed, the process of meiosis. If we look back at Fig. 11, we can see that when the chromosomes pair at the beginning of meiosis—at the time when crossing over must take place—each chromosome is already duplicated.

Now at any given level of a chromosome pair, crossing over takes place only between two strands out of the four, and always between two strands of different origin—never between the strands that have just arisen by duplication from one. Let us see, in Fig. 32, what effect this will have.

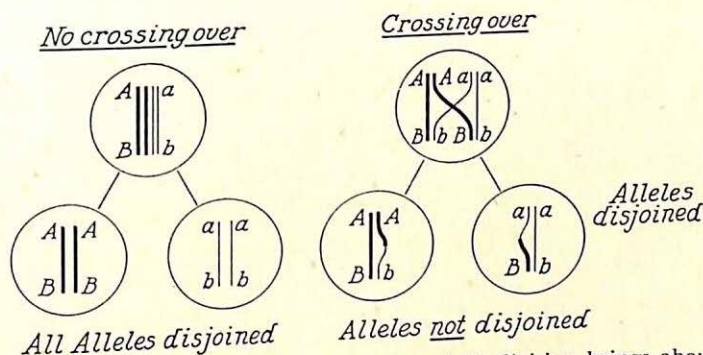


FIG. 32. Diagram illustrating how the first meiotic division brings about the segregation of all alleles when there has been no crossing over, but of only some of them (A and a , but not B and b) when crossing over has occurred.

Mendel established the principle that the effect of meiosis is to segregate alleles. From Fig. 32 it is evident that this can be accomplished for all pairs of genes at a single cell division only when there is no crossing over. With crossing over, some (A/A and a/a) will segregate; others (B/b and B/b) will not. It takes the second meiotic division to provide for the segregation of the latter (see Fig. 33), forcing us

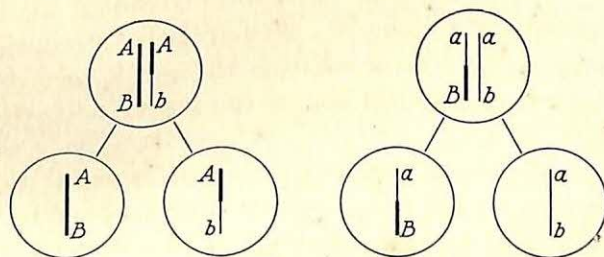


FIG. 33. Diagram illustrating how the second division of meiosis accomplishes the segregation of those alleles (B and b) that have not segregated in the first division because of crossing over.

to qualify the statement made earlier (p. 15) that each chromosome segregates from its homologue at the first meiotic division. With crossing over to take into account, chromosomes can no longer be considered as unbreakable units, and segregation, to be effective for all pairs of alleles, must regularly require two cell divisions.

We have seen that meiosis and syngamy, with their subsidiary phenomena of crossing over and linkage, are the major processes in the formation of the hereditary pattern of an individual. Through them come about the myriad varieties of individuals found in most sexually reproducing plants and animals. It is only in their light that we can comprehend the broader significance of sex, so potent a factor in the evolution of life-forms and in the individual lives of each of us. We have next to explore the ways in which the advantages of meiosis and syngamy to the race have been combined with the reproductive function, and to see how the division of labor between male and female has been steadily extended from the gametes to include an ever greater share of the life cycle. Gradually organisms have acquired a sure genetic means of determining sex, replacing the haphazard action of external environment or the vagaries of developmental forces alone. We cannot adequately comprehend the nature of the hereditary pattern until we see how this is accomplished, and until we see what effects the new mechanism has in turn on the transmission of the genes.



CHAPTER III

The Genetic Basis of Sex

SEX is a vital and productive force in man's life. Many have considered it, from a wide variety of viewpoints, without appearing to have grasped its basic significance as a biological phenomenon. Indeed, it was not possible to do so until the genetic and cytological advances of the present century had paved the way. Yet how futile it must be to carry the quest for the meaning of sex into obscure realms of emotion or social influence without that sure sense of direction which can come only with an understanding of its biological function and evolution.

THE MECHANISM OF SEX PRODUCES VARIATION AMONG OFFSPRING

Sex to most of us means "man and woman." Biology can, first of all, enlighten us as to this interpretation. Were we to make even a hasty survey of living organisms, it would become apparent, first, that all sexual characteristics are associated with the production of either sperms or eggs. Maleness is essentially the capacity to produce sperms; femaleness, to produce eggs. Second, we would see that an isolation of these two capacities in distinct individuals is a matter of secondary importance in the story of sex. Among many of the lower animals, each individual has two sets of reproductive organs, one male, the other female, and is therefore able to produce both kinds of gametes. Among the higher plants

this situation is by far the most general. The diploid seed plant generally either bears flowers carrying both male and female structures, or it has separate male and female flowers. Relatively infrequent are those plants, like the willow, whose male and female flowers are produced on entirely distinct individuals. An isolation of the sexes evidently cannot be regarded as the most widespread or essential feature of sex; it is important, to be sure, and we shall return to a consideration of its significance, but it is not "elemental" sex.

Nor does sex as a process necessarily imply cross-fertilization. Usually, of course, two individuals participate, even among hermaphroditic forms, such as the earthworm, where each individual possesses both male and female reproductive organs. But self-fertilization is quite the rule among many of the higher plants, such as the members of the pea and bean family, where the very possibility of cross-fertilization may be virtually excluded by the structure of the flower. Among one-celled organisms we can find an even clearer example of obligatory self-fertilization. *Actinophrys sol* is one of those heliozoans which, with their hundreds of delicate projections, look like indescribably dainty Christmas tree ornaments (Fig. 34); at times it interrupts the series of fissions by which it reproduces and engages in a sexual interlude. Two nuclei form by mitosis within an undivided cell mass. Each then passes through the usual two meiotic divisions, and following each, one of the resulting nuclei degenerates. Two haploid nuclei are left. These, the equivalents of gametes,¹ move toward each other, meet, and fuse. A zygote has thus been

¹ In one-celled organisms, a modified form of syngamy known as *conjugation* is frequent. In this process, two individuals make contact by a bridge of protoplasm. Then, following meiosis in each, an exchange of haploid nuclei takes place, a "male" nucleus from one individual wandering over the bridge to unite with a passive "female" nucleus of the other. One or both of the conjugants, depending on the species, resumes the normal vegetative life and the customary reproduction by fission. The process, as commonly described for *Paramecium*, is in most of the textbooks. Its biological effect is exactly that of syngamy, of which, in fact, it is no more than an interesting variant, one in which the gametes are nuclei instead of whole cells, and in

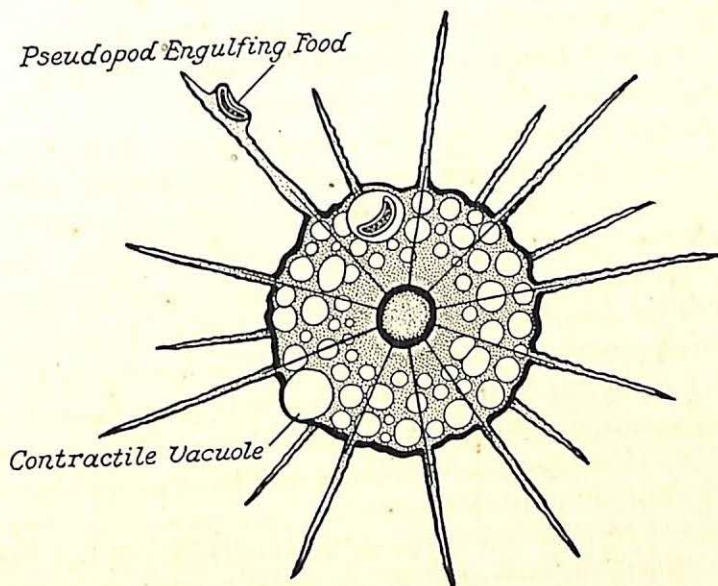


FIG. 34. The common heliozoan, *Actinophrys sol*. Its raylike pseudopods are temporary projections of the protoplasm used in locomotion as well as in engulfing food. The contractile vacuole eliminates excess water and some wastes. (From Buchbaum's *Animals without Backbones*. Courtesy of The University of Chicago Press)

formed by the union of gametes derived from the same "grandparental" cell.

If neither differentiation of the sexes nor participation of two individuals is the most universal aspect of sex, what element of sex is most fundamental? The answer should now be clear to us; it was the major subject of Chapter II—the cycle of meiosis and syngamy. Sex is fundamentally the adaptation of the individual to this cycle. *It is the capacity to form haploid gametes which later fuse.*

If this is so, it becomes clear that sex has often been confused as to meaning and significance. It is not, for instance, equivalent to reproduction. Mitosis results in two cells being

which three divisions, instead of the usual two, are required to form them. Only two of these divisions are meiotic; the third is an ordinary mitosis. Perhaps this situation is related to the original differentiation of spores and gametes, as in *Chlorogonium* (see pp. 124-125).

formed from one—that is the basis of reproduction, as was pointed out in Chapter I. Syngamy results in one cell being formed from two—that is the basis of sex. The two processes are diametrically opposite. Yet, in the origin of individuals of most forms, both play a part; and so interrelated are they that, to most of us, the function of sex has, no doubt, appeared to be reproduction. Instead, if its function is none other than that of the “meiosis-syngamy” cycle, it must be *the production of variation among the individuals of a family, of a population, of a race, of a species.*

SEXUAL REPRODUCTION RESULTS FROM THE INTERLOCKING OF SEXUAL AND REPRODUCTIVE CYCLES

Aside from cell division, there is, as we have already noticed, another essential component of reproduction. Cells, newly formed by the process of cell division, must loose their hold upon one another, must break their ties with parent organism and sister cell, and venture forth to start life on their own.² Organisms, whether haploid or diploid, generally arise from a single isolated cell. The haploid organism comes from a single haploid cell which we may call a *spore* (a term, to be sure, usually somewhat more restricted in its meaning). The diploid organism arises from a zygote formed by the fusion of two haploid gametes; in other words, a requirement of syngamy has been superimposed upon the isolated reproductive cells. In all other respects these two sorts of reproductive cells, spores and gametes, are extraordinarily similar.

If we compare spore and gamete formation in *Chlorogonium*, the simplest of the three members of the *Volvox*

² Sometimes, of course, the final severing of these ties is put off for a long time, while the young grow at the expense of their parents, receiving sustenance, care, and protection. This may even go so far that the offspring become permanently parasitic upon the parent organism (for example, the diploid phase of the life cycle in the mosses or the haploid phase in the seed plants). It is amusing to compare with these the lifelong economic dependence of children upon their parents in certain strata of our own society.

order that served in Chapter I (p. 45) to illustrate the progressive limitation of reproduction to special reproductive cells, we can get a good idea of their extreme similarity. (Meiosis immediately follows syngamy in these algae, as in *Spirogyra* (p. 126), so that all the cells spoken of here are haploid.) In *Chlorogonium* each individual divides into four cells. These then break out of the envelope of the parent, and become independent individuals; in other words, they are spores. However, sometimes a third cell division doubles this number before they are set free, and these half-sized individuals, otherwise identical with the spores, behave as gametes. Each must fuse with another gamete before resuming cell division; otherwise it perishes. From the resulting zygote there forms a cyst which enables the organism to survive adverse conditions, and from it, by meiosis, there will arise four vegetative individuals (see Fig. 8A, p. 54). In simple forms like this, gametes and spores are frequently indistinguishable. The similarity goes even further, as we shall see later (p. 133).

There is, indeed, but one real distinction between spores and gametes. The former can begin cell division autonomously if external conditions are favorable; but gametes must normally undergo fertilization before cell division and development can start. In the gamete, mitotic activity is blocked. In the spermatozoon, this might be due simply to its lack of cytoplasm and foodstuffs. The ovum, however, has no lack of these, and the obstruction must be of another sort. Just what, we cannot say, although we do know that it can be removed by agents other than the entrance of a sperm. In some of the algae and in many animal ova, even in those of mammals, development may be activated by a great variety of causes.³

There is great variety in the time at which this block, the

³ Salts, acids, alkalis, hypertonic solutions, temperature change, electrical stimulation, shaking, puncturing with a needle, are examples. However, what works with one egg often will not work with another, even though they are closely related.

occasion of syngamy, occurs with respect to meiosis. As meiosis is a consequence of syngamy and cannot be understood except as a complement to it, we might expect it to follow syngamy immediately. This, however, is not so in the higher animals and plants, and we have to turn to primitive organisms to find such a situation. Although, so far as is known, this sequence occurs in only two of the protozoa (a sporozoan and a gregarine), it is frequent in the lower plants, such as desmids and diatoms, and especially in the conjugating algae. In *Spirogyra*, the familiar filamentous green alga with the spiral chloroplast, two strands may often be observed "conjugating." A bridge of protoplasm forms between adjacent cells of the two strands, and the entire substance of one cell, cytoplasm as well as nucleus, passes over the bridge and merges with that of the other. Then the nuclei fuse. This, of course, is syngamy, and a diploid nucleus results. The zygote thus formed is set free from the filament, and forms a cyst, capable of withstanding unfavorable conditions, such as drought or winter weather. Whenever vegetative growth again becomes possible, the cyst (zygote) germinates. *Its first two divisions are the meiotic divisions.* Of the four nuclei thus formed (the cytoplasm is not divided up), three degenerate. Then, from the cell with its one remaining haploid nucleus, there is produced by mitotic cell division a typical filament, all the cells of which are likewise haploid.

We have seen that the cycle arising from the act of syngamy is: syngamy→diploid constitution→meiosis→haploid constitution→syngamy again. To compare the relative length and importance of these alternating diploid and haploid phases of the life cycle in *Spirogyra*, we can best resort to a diagram (Fig. 35).

In higher plants, the haploid phase gradually gives way to the diploid, and intermediate forms exist which have a marked alternation of haploid and diploid generations. These may be diagramed in a similar way (Fig. 36). In these

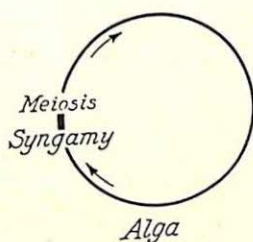


FIG. 35. The relative lengths of the haploid and diploid phases of the life cycle in the common green alga *Spirogyra*. Haploid, thin line; diploid, thick line.

life cycles meiosis takes place just before the formation of spores. The diploid plant accordingly produces spores; it is the *sporophyte*. The plant of the haploid generation then produces gametes and is called a *gametophyte*. The diploid and haploid plants are usually quite different, so much so, in fact, that in one brown alga (*Cutleria-Aglaozonia*) they were actually considered different genera until the life cycle was worked out.

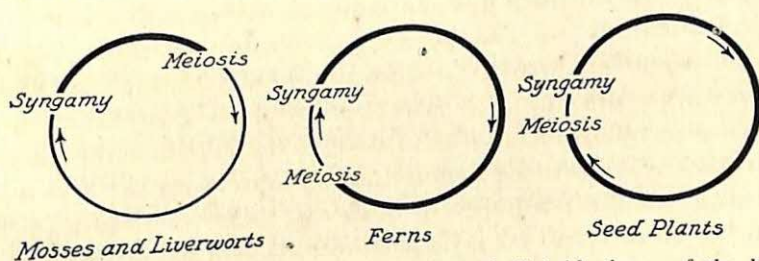


FIG. 36. The relative lengths of the haploid and diploid phases of the life cycle in mosses and liverworts (bryophytes), in ferns (pteridophytes), and in seed plants (spermatophytes). Haploid, thin line; diploid, thick line.

However, it is not the alternation of generations of haploid and diploid multicellular forms that in itself interests us here. A comparable alternation does not exist in animals. Nor is there any real connection between the vegetative forms and the chromosomal constitution. This is known from the fact that, by suppressing meiosis, *diploid* "gametophytes" can be produced, and by stimulating unfertilized eggs to develop, *haploid* "sporophytes" can be obtained, in each case the re-

verse of their normal chromosomal constitution. The important consideration is that this alternation reveals plainly that the immediate production of gametes is not the invariable result of meiosis. Meiosis produces haploid reproductive cells, but these are typically "spores."

As the importance of the haploid phase is progressively diminished from the lower plants to the higher, the gametophyte is finally reduced to two or three cell divisions parasitically dependent upon the sporophyte.⁴ Yet even here meiosis does not result directly in the production of gametes.

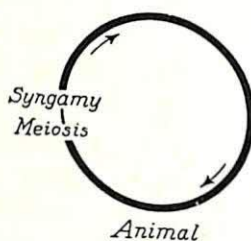


FIG. 37. The relative lengths of the haploid and diploid phases of the life cycle in animals. Haploid, thin line; diploid, thick line.

In animals, on the other hand, the gametes are the product of meiosis itself. The whole difference between the sexual cycle of animals and that of the various plants lies here. Yet it is not, after all, more than a minor change, even though it results in the restriction of the haploid phase of the life cycle to the gametes themselves. A diagram representing the situation in animals (Fig. 37) is very much like Fig. 36, which represents the situation in the higher plants.

The production of gametes by the meiotic divisions is the result of synchronizing the block to mitotic activity and meiosis. Yet even among animals, just as among plants, there

⁴ The superiority of diploidy, on account of its insurance against the deleterious effects of mutated genes, has no doubt been a major factor in the evolution of plant life. The alternation of haploid and diploid generations does possess definite evolutionary advantages; but wherever, as in the higher plants, there appear in the diploid phase of the life cycle such mechanisms (self-fertilization; vegetative propagation) as provide the same advantages we find in the haploid gametophyte (namely, rapid expression of new recessive mutants and breeding true to type), then the gametophyte tends to become vestigial.

is no exact uniformity in the time at which this block occurs. It varies considerably in its incidence; it may fall just before, during, or just after meiosis. Table II shows that even among closely related types there is no uniformity.

TABLE II

<i>Incidence of block</i>	<i>Type of organism</i>
1. After ovum is mature	Higher plants; sea urchins, coelenterates (rare in animals)
2. During second reduction division (at metaphase or anaphase)	Some invertebrates; many vertebrates — frog, mouse, bat, etc., probably man
3. During first reduction division (at metaphase)	Many invertebrates (various worms, insects, mollusks)
4. Before reduction	Common in invertebrates (various mollusks, crustaceans, worms)

The incidence of the block relative to the meiotic process is one of the hereditary characteristics of each particular organism. In other words, genetic factors control the time at which the block intervenes. This is an important fact, since it follows that the alternation of haploid and diploid generations characteristic of the plant kingdom and the relative absence of a haploid stage in animals are not, as might seem at first, fundamentally remote sorts of life cycles. To put it another way, a rather simple genetic change, a mutation or so, might entirely remove this block to development in the reproductive cells formed by a diploid animal, and thereby transform these cells from gametes to "spores" and introduce a haploid phase into the life cycle.⁵

⁵ *This has actually occurred.* In bees, ants, and wasps, and among various other invertebrates, eggs may develop without having been fertilized. These eggs are, then, equivalent to spores, for they are reproductive cells lacking that block to developmental activity which is characteristic of gametes. Like the haploid phase of the plant's life cycle, the haploid individuals developing from these unfertilized eggs produce gametes which require syngamy. This situation, known as *haploid parthenogenesis*, is linked with the mode of sex determination in these insects, so that the haploid individuals are male.

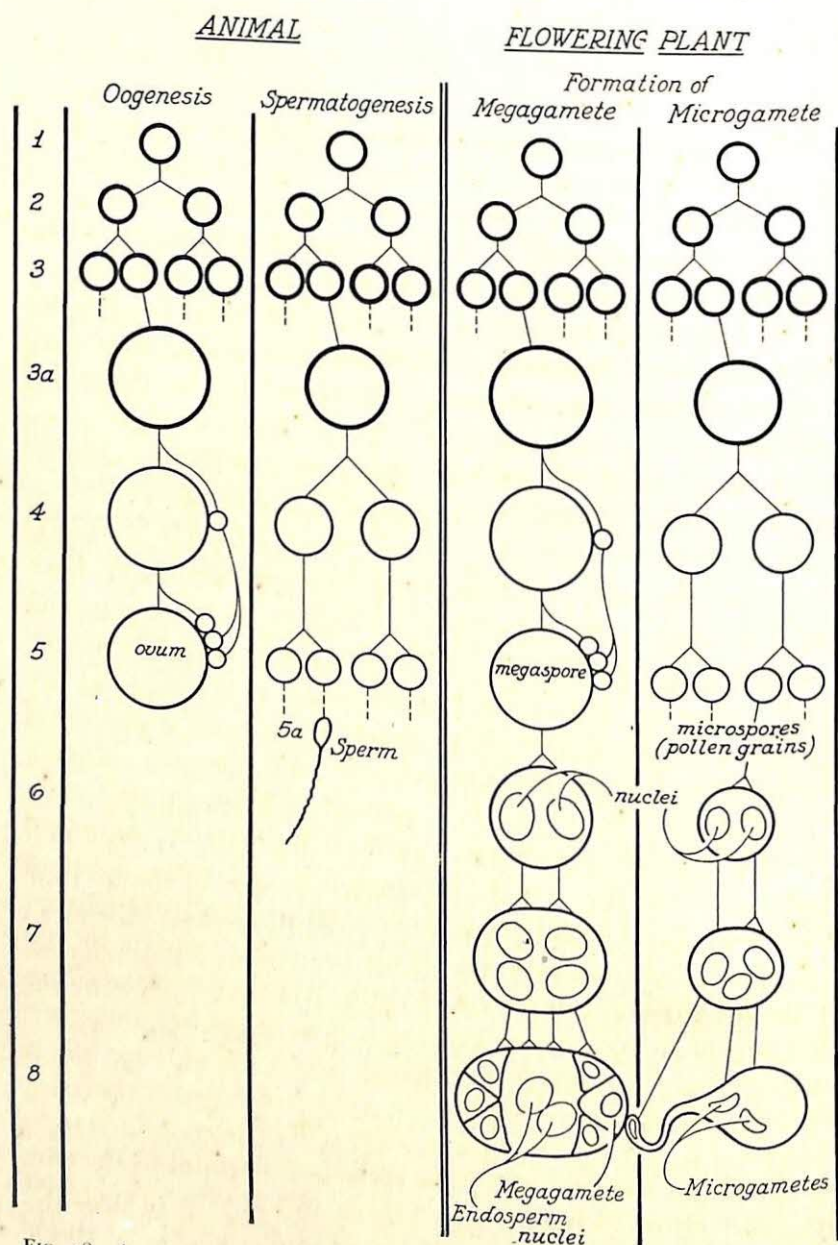


FIG. 38. A comparison of gamete formation in animal and flowering plant. For explanation see text, pages 131-133.

*Gamete formation is similar in animals
and higher plants*

From what has been said, it is clear that the formation of the reproductive cells in the higher plants is quite similar to that of animals. Figure 38 makes this clear, similar stages being placed on the same level, with diploid cells indicated by thick lines and haploid by thin lines.

The first three horizontal rows are evidently alike in all four columns. The two cell divisions represented here merely indicate that each prospective reproductive cell has a lineage which goes back to the diploid zygote formed by syngamy, a lineage which, through an indefinite number of cell generations, consists of undifferentiated cells.

We may really start, then, from any single cell in row 3. These are the cells which will undergo meiosis. First, however, each passes through quite a long period of growth and food storage; and here we can notice the first difference between our columns. The growth and storage of food are greater in the prospective female gametes of both animals and seed plants than in the prospective male gametes. Row 4 shows the products of the first meiotic division. In the male lineages the cells which are produced by division are equal in size, but in the female lineages one cell receives all of the stored food, plastids or other organized cell structures, and most of the protoplasm. This is brought about by the particular orientation of the spindle. When the spindle lies close to the surface of the cell (as it does whenever there are present large amounts of inert substances, such as food, which impede cytoplasmic division), it makes a great difference whether the axis of the spindle is parallel or perpendicular to the surface of the cell: for if the spindle is parallel to the surface, the cell offspring will be equal; but if it is perpendicular, the outer cell will be very small, and the other, which will be very large, will get all the stored substances. Both kinds of orientation occur, each in an appropriate situation.

When, during cleavage of the zygote (see Chapter V, p. 226) it is vital for each cell to get its share of the food needed for the activities of cell division and development, the spindle regularly lies parallel to the surface of the cell. But when, as here, the life and growth of a new individual depend upon the sufficiency of the food contributed by the ovum, the spindle is perpendicular, and the stored food supply is not divided up (see Fig. 63). As a result, each animal ovum is accompanied by three tiny, functionless *polar bodies*; and the megagamete of a flowering plant, typically, by three vestigial megagametes. On the other hand, in the male lineages each of the quartet of haploid cells produced by meiosis is functional. In animals these differentiate into spermatozoa without further cell division (Fig. 38, row 5a); in the plant they are the *pollen grains*.

Figure 38 shows three more cell generations in the female lineage (rows 6, 7, 8), and two more cell generations in the male lineage (rows 6, 7) of the flowering plant. These represent the growth of the vestigial haploid phase of the life cycle (the *gametophyte*). The three divisions of the megaspore produce an oval *embryo sack* of eight cells. Five of these are accessory and play no important role. Two nuclei in the center remain in an undivided mass of cytoplasm which contains most of the stored food of the megaspore; these are the *endosperm* nuclei. The eighth cell, at one end, is the megagamete.

Within the pollen grain there are produced two microgametes and one pollen tube nucleus, but the cytoplasm of the pollen grain is not divided up. When the pollen grain alights upon the stigma of a flower of its own species, it commences vigorous growth, forming a pollen tube which penetrates the stigma and eventually reaches the embryo sack of an ovule. As it grows, the pollen tube nucleus stays at the tip; when its work is done it degenerates. The microgametes also move down the pollen tube as it lengthens and, when the embryo sack is reached, penetrate it. Here occurs

the peculiar fertilization mentioned earlier (p. 62 *ftn.*), with one microgamete fusing with the megagamete to form a zygote, the other fusing with the two endosperm nuclei to form the triploid endosperm.

The similarity of spores and gametes is very striking here. Spores from each plant cell undergoing meiosis are typically produced in groups of four (row 5 in Fig. 38), although by a succeeding mitosis or two they may, in some organisms, be further increased in number. In animals, gametes are also typically formed in quartets, although in a few organisms extra divisions multiply their number also. In many plants spores are differentiated, like gametes, into large and small, the large producing a female haploid plant, and the small, a male (row 5, Fig. 38). Moreover, three of the four megaspores in a group generally degenerate and only one is functional; just as, when each animal ovum is being formed, three nonfunctioning polar bodies accompany it (rows 4, 5, Fig. 38). The transportation of the reproductive cells of the male line to the female line occurs in both animals and seed plants between rows 5 (5a) and 6. Hence, in the former, gametes are transferred; in the latter, spores (pollen grains)—yet another instance of parallelism.

In these ways the sexual cycle is superimposed upon the reproductive cells. Syngamy removes a block to mitotic activity, a block which differentiates gametes from spores. This block may be shifted by minor genetic changes. Thus there arise forms with alternating haploid and diploid phases of various lengths and degrees of importance (higher plants). When the block is imposed during meiosis, the entire haploid phase is eliminated, except for the gametes themselves, and we have the purely diploid individuals characteristic of the animal kingdom.

“IN THE BEGINNING . . . MALE AND FEMALE”.

In all but the very simplest organisms gametes can always be distinguished as either male or female. Although among

lower organisms, such as diatoms and green algae, amebas and ciliates, gametes usually cannot be clearly recognized as male or female, in many of these the fusing gametes are readily distinguishable by differences either in size and form, or in activity. In *Mucor*, a bread mold, for example, all the threads look alike. Yet they are different physiologically, for not all strands will conjugate; that is, only the gametes of certain strands are different. It is, indeed, very questionable whether there are any organisms in which fusing gametes are both physiologically and morphologically alike. It appears probable that the impulse toward syngamy depends upon the existence of unlikeness, that the very foundation of sex is an affinity of unlike forms. Of course, not too unlike! Male and female gametes show decreasing affinity for one another as they come from species more and more distantly related. But even sperms and ova of different phyla seem to have some affinity for one another—for example, those of mussels and sea urchins.

Sexual differentiation can be found even within the most closely related cells. Some authorities on the subject maintain that it is a universal phenomenon among sexual organisms that *every individual, and indeed every cell, possesses the potentialities of both sexes.*⁶

It has been discovered that in the flagellates two "sex substances" are given off into the water and may be obtained apart from the organisms by filtering them off. It is also claimed that these two substances are produced by every individual, but that groups of individuals differ in the relative proportions of the two substances they secrete. Hence the organisms can be grouped into "mating types," individuals of one mating type pairing only with others of a not too

⁶ Hartmann, Max. *Verteilung, Bestimmung, und Vererbung des Geschlechts bei den Protisten und Thallophyten*. "Handbuch der Vererbungs-wissenschaft," No. 9. This monograph on sex determination in primitive forms of life will undoubtedly prove stimulating to those who can read it. Like the other monographs of this most authoritative series, it has, unfortunately, never been translated into English.

similar type. In other primitive organisms (fungi, *Paramecium*) "mating types" have also been discovered. Sometimes there are only two in any local group, but again there may be more. Whether or not we regard the latter situation as a multiplicity of sexes, there seems to be ground for believing that these differences of mating type are all based upon a chemical bipotentiality, so that we may speak of a "male" and "female" principle, although perhaps we cannot term particular mating types definitely male or female.

These chemical principles of sexuality that are responsible for the act of syngamy are not necessarily identical with those which underlie the differentiation of gametes into a large, nonmotile female type and a small, active male type. This appears to be the case from observations that large "female-type" gametes may pair with those of a different mating type which are, nevertheless, also large and apparently "female" in type. Definitions of sexuality become exceedingly controversial when applied to primitive forms. We can only reach agreement upon the application of the terms *male* and *female* wherever the mating types are reduced or limited to two and where these produce mega- and microgametes, respectively.

Among all definitely sexual species, a second sort of bipotentiality appears to be a fundamental characteristic; that is, the capacity to produce both male and female gametes is present in each individual, although it may not be developed or exercised equally. This is evident in the great majority of plants and is well-nigh universal among the more primitive ones. The lower animals, too, are nearly all hermaphroditic; and among those more specialized types characterized by isolated sexes, such as insects and mammals, intersexuality and sex reversal are sufficiently frequent to impel us to believe that bipotentiality is a rule there, too.

Whether we are dealing with the first or the second type of sexual bipotentiality, we can safely assume that either is due to genetic factors, just as we assume that these underlie

all developmental potentialities; and we may symbolize them by letters, keeping in mind, however, that they probably represent gene complexes rather than single genes. Letting M represent the potentiality for maleness and F that for femaleness, the basic genotype as to sex is then MF when haploid, MMFF when diploid.

Most evolution has tended to increase the organism's control over its own internal environment—over its basic life-processes. The ultimate step in this direction is to superimpose the internal, stable biological control provided by genes upon the haphazard, less easily regulated determination by the environment. Sex being one of the basic life phenomena, it is not surprising that, in the course of organic evolution, genetic factors have arisen which react with, or even replace, nongenetic ones in controlling the time and mode of sex determination.

First there seem to have been established genes controlling the incidence of sex determination (that is, its time in the life cycle and its place within the organism); for in a great many animals and plants this is all that has ever developed. Occasionally the determination of which cell or group of cells shall be male and which shall be female is left largely to the mercies of the external environment. For example, most larvae of *Bonellia*, a marine worm, when isolated become females; but a larva that finds a female becomes attached to her proboscis, develops there into a tiny, parasitic male, and ultimately lives within the female's uterus. In the horsetail (*Equisetum*), strong light and plenty of nutriment lead to the development of exclusively female sex organs, while the lack of these environmental factors results in male sex organs. In other plants certain soil conditions tend to exert a similar sex-determining effect.

However, like other developmental traits, sex is generally controlled through the internal environment by the action of certain parts of the organism upon other parts. The little moss *Funaria* affords us a relatively simple example of this

situation. Each haploid spore of *Funaria* germinates into a plant with two branches, one apical, the other lateral. The apical branch is always male, the side branch female, while the stalk on which they grow is neuter. Now, the differentiation of the one branch as male and the other as female is, no doubt, a matter of reciprocal relations; but the fixation of the time and place at the moment of branching is a species characteristic, hereditary, and, we therefore assume, genic.⁷

In *Funaria* sex differentiates in the course of the haploid phase. The diploid plant which grows from the zygote is, like the haploid plant in early growth, sexually bipotential and neuter. Many ferns and mosses are like *Funaria* in this respect. On the other hand, if genes impel sex to differentiate at some time during the diploid phase, the differentiation then persists through the haploid phase, too. Among plants the higher ferns and a large majority of the flowering seed plants, and among animals the coelenterates, flatworms, and annelids all fall into this group. This situation is probably the most universal in respect to sex.

Considering plants first, we find that many, such as the pea and the bean, the rose and the lily, have flowers which contain both male and female organs, the stamens and the pistils, respectively. Here sex makes its appearance during the formation of the flower. Next there are a few plants, such as the horse chestnut, which have some flowers mixed, some pure. The horse chestnut, for instance, has mixed flowers and pure male flowers on the same tree, so that sex becomes differen-

⁷ It is not at all plausible that most fundamental inherited characteristics of a species are nongenic, and that minor variations monopolize the most effective means of cellular division, mitosis. There is a good reason why we cannot prove the genic nature of the major characteristics of any given form of life. Because they are so vital a feature, any change in the genes governing them is almost certain to lead to a condition that will be lethal during development; such mutations are immediately eliminated. These genes are consequently kept homozygous. But through meiosis and syngamy we are able to trace only heterozygous pairs of genes. We are dependent upon differences between alleles for our knowledge of each specific gene. It is, therefore, quite probable that we shall never be able to identify many of those which are most important.

tiated sometimes during flower formation and sometimes just before. (However, each plant species is quite constant in the kinds of flowers a single plant will bear.) Transitional forms such as these lead us to a type where the flowers on a plant are all either pure male or pure female, though both grow on the same plant. This condition is probably as familiar to us as the first—think, for example, of the squash and cucumber, maize, chestnut, beech, and birch.

In hermaphroditic animals, sex is usually distinguishable only in the sex organs. These are often present simultaneously, as in the earthworm; in other forms, such as the common *Hydra*, they are not present together, except rarely, but arise at different seasons.

Sex differentiation may thus fall early or late in the diploid, as well as in the haploid, phase. The very fact that it may occur *during* the phase shows that it is not a phenomenon of chromosome segregation, which occurs only at meiosis. The genes determining its time and place must normally, therefore, be homozygous—and in this respect sex differentiation is no different from that of any other developmental trait (see Chapter V). To portray the situation we may, then, represent the genotype of the sex-gene complexes as MFZ in the haploid phase and MMFFZZ in the diploid, letting Z stand for those genes which fix a characteristic time and place for sex differentiation in each species or variety. This may be expressed in a diagrammatic way (Fig. 39) in connection with the haploid-diploid life cycle. The genes represented by Z may be envisaged as the alarm hand of a clock, pointing to the time in the cycle when sex is realized—when, if haploid, MF becomes (M)F and M(F) in different parts of the body, or, if diploid, MMFF similarly becomes (MM)FF and MM(FF).

THE SEXES ARE NEXT ISOLATED

Complete isolation of maleness and femaleness appears to have arisen from hermaphroditism. In some plants, in many

invertebrates, and even in some fishes, sexuality is consecutive or alternating. In some of these forms the individual first passes through a functional male phase, next matures as a female, and then may revert to a final condition of maleness, or, like the common oyster, may continue to vary back and forth with the seasons. The same primitive germ cells

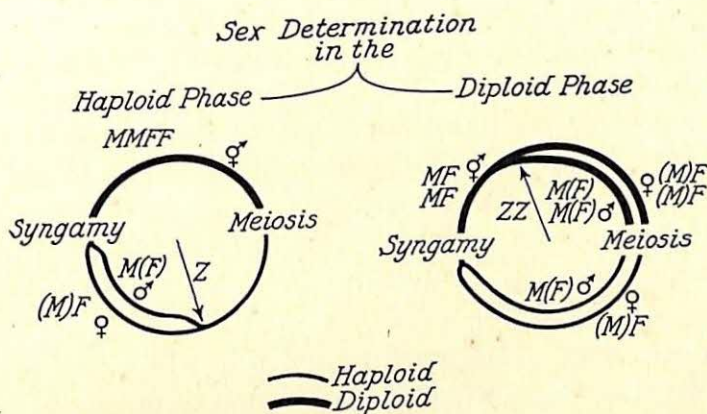


FIG. 39. Sex determination in the haploid phase, as in the moss *Funaria*, contrasted with sex determination in the diploid phase, as in maize (*Zea*). ♂ = sexually undetermined; ♂ = male; ♀ = female. M, genes for maleness; F, genes for femaleness; Z, genes controlling the time and place of sex determination in the life cycle. The "alarm hand" indicates the time at which sex is determined. The symbols for the M and F genes whose effect is locally and temporarily inhibited are placed in parentheses.

are able to develop either into sperms or into eggs, depending upon the sexuality of the reproductive organs, and during the course of sex reversal self-fertilization may even occur.

In other forms, such as *Crepidula*, a marine snail, the female phase, once it is attained, persists throughout life. Since male and female gametes do not mature together during sex reversal, self-fertilization is prohibited. Here, then, in contrast to the preceding instances of but partial isolation of the sexes, functional maleness and femaleness do not coexist in the same individual. Like change of plumage in a fowl from

an immature to a mature phase or like metamorphosis in insect and amphibian, this consecutive type of sexuality is governed by homozygous genes, in the manner described in the preceding section.

However, most organisms have hit upon a simpler mechanism for bringing about the isolation of maleness and femaleness. Not only can sex be determined by genes acting either during the haploid or during the diploid phase of the life cycle, but it can also be determined *at* the time of change from one phase to another, that is, at meiosis or at syngamy. This latter situation, of particular importance among the higher animals, has far-reaching effects. It brings about, besides the isolation of maleness and femaleness in separate individuals, the inheritance of nonsexual traits in association with sex, and a maintenance of the sexes in an approximately equal ratio. Let us see how this is brought about.

In the first place, if sex determination falls at meiosis, the sexes will, as a consequence, be isolated throughout the entire following phase; that is to say, haploid individuals will be male or female and not neuter or of mingled sex. This is true of certain ferns.

If, on the other hand, sex is determined at syngamy, isolation is complete for the whole diploid phase and carries over through the entire succeeding haploid phase as well. Among the seaweeds of the genus *Codium*, we may trace the evolution of such a step. There is one species (*C. decorticatum*), the diploid plants of which bear both male and female sex organs. In another member of the group (*C. elongatum*), both kinds of sex organs grow sometimes on the same plant, at other times on different plants, apparently depending upon the season of the year. In yet other relatives, male and female sex organs grow only on different plants; that is, the sexes are quite isolated from the time of syngamy on. Another example, in a more familiar organism, is found in maize. Several mutant genes have been found which in combination can

convert the normally monoecious^s Indian corn into a type with isolated sexes (see p. 145).

The determination of sex at meiosis or syngamy may be brought about environmentally, as in *C. elongatum*, but in most known cases it is genetic. We might indicate this in Fig. 39 merely by shifting the "alarm hand," representing the action of genes which fix the time of sex determination, until it points either to meiosis or to syngamy. However, such genes are rarely homozygous. They are, as a rule, heterozygous, and sex is determined by their segregation and recombination.

Before we go on to trace this behavior, it will be well to ponder for a moment the significance of the separation of maleness and femaleness. From childhood we are acquainted with the fact that they are completely isolated among all the higher animals, while, on the other hand, this isolation is comparatively rare among the higher plants. What are the consequences of these opposed systems, both of which are apparently so successful, so widespread?

An isolation of the sexes obviously makes the closest kind of inbreeding, self-fertilization, impossible. The converse situation permits it. Our question, then, resolves itself into the relative genetic and evolutionary merits of inbreeding and outbreeding. What reasons lie back of the almost universal prohibition of brother-sister marriages among human societies? Why does a stockman, on the other hand, constantly use this very type of cross, or the even closer one of parent with offspring, when he wishes to breed a choice variety? Among plants with perfect flowers, which are presumably capable of self-fertilization, why is there so widespread a dependence upon winds and insects to insure cross-fertiliza-

^s *Monoecious* and *hermaphroditic* are the two terms used, respectively, by botanists and zoologists to describe the production of both male and female gametes by a single individual. *Dioecious* is the only term describing the complete isolation of these sexual capacities in distinctly male or female individuals.

tion? Is there any reason for us to frown upon cousin marriages? Is there any biological justification for the elaborate totem system of the northwestern Indians, which insured their marrying outside their own clan? Is it equally good, better, or worse, to marry always within the "family" or the native village?

To answer these questions, we must probe the genetic effects of self-fertilization. A homozygous individual, $AABB$, will form only AB gametes, and, if self-fertilizing, only $AABB$ homozygotes like the parent can be produced. A heterozygous $AaBb$ individual forms, as we have seen (Chapter II, pp. 98 ff.), four types of gametes. Upon self-fertilization, these will produce nine genotypes in various proportions. Four ($AABB$, $aabb$, $AAbb$, and $aaBB$) are homozygous, and, when self-fertilized, will breed true. Assuming random assortment these will on the average make up one fourth of the progeny. One half of the offspring are homozygous for one gene pair, but heterozygous for the other. These, when self-fertilized, will yield one half homozygotes, one half heterozygotes for one pair of genes. The remaining one fourth of the original progeny are, like the parent, heterozygous for both pairs of genes, and when self-fertilized, will give once again one fourth homozygous, one half homozygous-heterozygous, one fourth heterozygous. Summing up, at the end of one generation of inbreeding, one fourth of the group are completely homozygous. At the end of a second generation the proportion is $\frac{1}{4} + (\frac{1}{2} \text{ of } \frac{1}{2}) + (\frac{1}{4} \text{ of } \frac{1}{4}) = \frac{9}{16}$. We can similarly calculate that at the end of a third generation it will be $\frac{9}{16} + (\frac{1}{2} \text{ of } \frac{1}{4}) + (\frac{1}{2} \text{ of } \frac{1}{8}) + (\frac{1}{4} \text{ of } \frac{1}{16}) = \frac{49}{64}$. Without carrying this farther, one can readily see that inbreeding very rapidly reduces a heterozygous group to the homozygous condition. Self-fertilization, being the closest form of inbreeding, merely does rapidly what other forms of inbreeding, such as brother-sister matings and cousin marriages, do more slowly.

Our many questions have thus been resolved into a single

one: Which is better, heterozygosity or homozygosity? The answer, of course, must depend upon the nature of the recessive genes present in the ancestor to begin with. If there were numerous beneficial ones and none markedly deleterious, inbreeding, by rendering them homozygous and contributory to the phenotype, would unquestionably be beneficial. Moreover, once an advantageous phenotype is obtained, it will breed true if it is homozygous and is inbred. Thus peas and beans maintain excellent stock by self-fertilization—homozygous lines of poor character having all been eliminated through selection. Thus, too, the Ptolemies of Egypt kept their fine line from deteriorating by brother-sister marriages, which produced the most enlightened rulers of their time, until, in Cleopatra, the dynasty ended with the most brilliant flower of all.

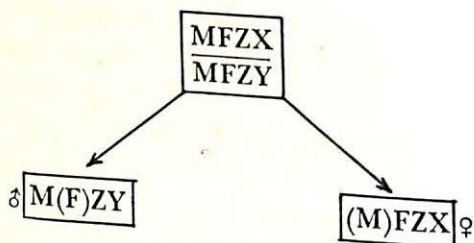
On the other hand, inbreeding renders homozygous all harmful recessive genes, too. The general prevalence of these can be recognized if we recall that most mutations are recessive, and that of these almost all are detrimental to some degree. Deleterious recessive genes are eliminated only very slowly by natural selection, and thus close relatives tend to carry them in common. This can be seen from the fact that the percentage of stillbirths and abortions in first-cousin marriages is far higher than in the general population, a situation due to recessive lethal genes being carried by both parents (see Fig. 14).

On the whole, inbreeding results in a merciless weeding out of harmful recessive genes. Populations which habitually inbreed have been purged. On the other hand, those which habitually crossbreed will not have been purged. Individuals in them must usually be heterozygous for harmful recessives; and inbreeding will, therefore, as a rule result in the emergence of the undesirable traits. The isolation of the sexes in distinct individuals merely prevents that closest form of inbreeding, self-fertilization. Since its advantage lies in preventing the emergence of harmful recessive traits, it probably

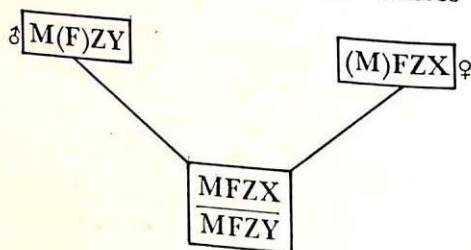
arose in evolutionary lines in which crossbreeding was already established and these deleterious traits were relatively numerous.

Having now examined the consequences of an isolation of the sexes in distinct individuals, we may turn next to the mechanism by which the isolation is brought about. If a pair of genes determining sex was heterozygous, one gene favoring maleness and its allele favoring femaleness, they would, of course, segregate at meiosis. The resulting haploid cells, carrying one or the other, would then be either male or female. To our diagram (Fig. 39, p. 139) we need only add such a gene pair, X favoring F (femaleness), Y favoring M (maleness).

Sex Determination at Meiosis



At syngamy, a male gamete and a female gamete of these two genotypes will unite, and the zygote is again heterozygous for X and Y. As when other alleles interact, the

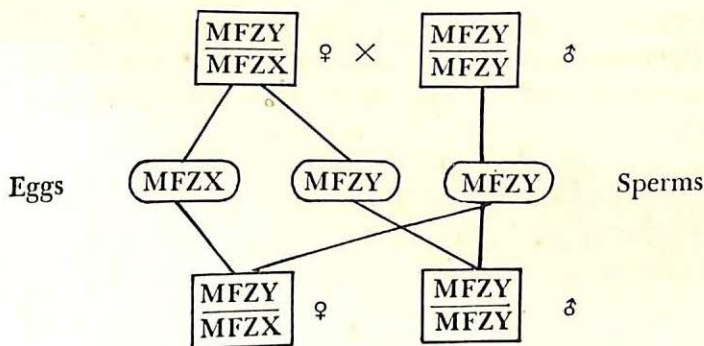


phenotype resulting here from the interaction of X and Y might be a blend, or one might be dominant over the other. Among protozoa, algae, fungi, and mosses, for instance, there

is generally a blending of the two, and the diploid phase is of a "mixed-sexedness." In a liverwort, *Sphaerocarpos*, however, the allele for femaleness is dominant, and hence the sporophyte is female.

Maize stocks with mutant genes capable of isolating the sexes represent another instance of this sort. One of these genes, *barren-stalk* (*ba*), a recessive, suppresses the development of ears, that is, of the female flowers. The *tassel-seed* (*Ts*) mutants (there are several, either dominant or recessive) convert the tassels, normally male flowers, into female ones. Thus a race segregating for dominant tassel-seed but homozygous for barren-stalk has separate male and female plants. The female (*Ts*/+; *ba*/*ba*) produces two kinds of gametes (*Ts*; *ba* and +; *ba*). The male (+/+; *ba*/*ba*) produces only gametes carrying +; *ba*. The sex of each individual of the next generation is then determined at syngamy by its genotype, which will depend upon the kind of egg being fertilized. Using Y for the recessive male sex gene and X for the dominant female sex gene (*tassel-seed*), we may diagram the situation as follows:

Sex Determination at Syngamy



The systems of sex determination we have just described will work efficiently only on one condition: There must be no multiplicity of such heterozygous sex genes as X and Y, for not only does meiosis bring about the segregation of al-

les, it also leads to the recombination of genes of different pairs. Random assortment of two pairs of sex genes would lead to four haploid combinations, or "sexes," and with each added pair the number would increase according to our now familiar formula, 2^n . Just such a sexual mélange seems to have arisen in the common black molds, many of which, apparently, have quite a number of "sexes." Only if all the sex-determining genes were in one pair of chromosomes (and if crossing over were also inhibited) could confusion be avoided. This solution to the problem seems to have been discovered more than once, and in some of the liverworts sex chromosomes (carrying these sex-determining genes) can actually be distinguished. Among the pairs of chromosomes, there is one made up of two different members. Sometimes one chromosome is a little smaller than its homologue, sometimes a great deal smaller, sometimes missing altogether. The haploid plants getting the large chromosome (commonly called the X-chromosome) are *female*; those getting the little homologue (the so-called Y-chromosome), or no homologue at all, are *male*.

Yet even these steps cannot guard against the greatest danger to the sex-determining mechanism—that of mutation. As long as a single pair of genes bears the entire responsibility for the regularity of sex determination, any mutation of the sex alleles might be fatal. Nor would the danger be limited to mutation of the existing sex genes. Mutation might give rise even more probably to other genes also having a sex-determining potency. Consider the state of the true-breeding bisexual (dioecious) maize race we have just described if a recessive tassel-seed mutant were also to arise in it and begin segregating!

Actually the situation here is of little importance to us, for it is not widespread. Nor is it likely that it was actually a step, unless a very transitory one, in the evolution of sex determination in the higher plants and animals. It most likely represents an evolutionary offshoot. Logically, how-

ever, its relative simplicity makes it easier for us to understand the more complex, yet similar, phenomena of our own mechanism of sex determination.

IN MAN AND THE HIGHER ANIMALS, A COMPLEX BALANCE
OF SEX-DETERMINING GENES IS HANDLED IN A SIMPLE
WAY BY MEANS OF SEX CHROMOSOMES

In the higher organisms there is a multiplicity of sex-determining genes, apparently scattered haphazardly among the various chromosomes. No doubt this is a consequence of the random nature of the evolutionary processes affecting the genes and chromosomes—mutation, translocation, and so forth. Since each diploid individual originates through syngamy, its sex must be affected more immediately by recombination than by segregation. Recombination following segregation, however, leads to a multiplicity of combinations, whereas two sexes are quite enough. How can this be avoided?

If we examine the chromosomes of males and females of some one of the higher animals, say, for example, a bug (*Lygaeus*) or a fruit fly (*Drosophila*) or, for that matter, a man, we can get an inkling of the answer. (Because *Drosophila* has the lowest number of chromosomes, it provides the simplest diagrams.) *Drosophila* females have four pairs of chromosomes, each pair made up of identical-looking homologues. In males, however, one of the pairs is composed of two obviously unlike mates. One of these, rodlike, corresponds to one of the pairs present in females; the other is shorter and hooked, like the letter J (Fig. 40). Following meiosis, all the eggs will carry similar sets of chromosomes, but the sperms will be of two kinds, some carrying the straight member of the differentiated pair (this one is the X-chromosome), and others carrying the hooked member of the pair (this one is the Y-chromosome). Syngamy will then result in two sorts of individuals, determined by the type of sperm

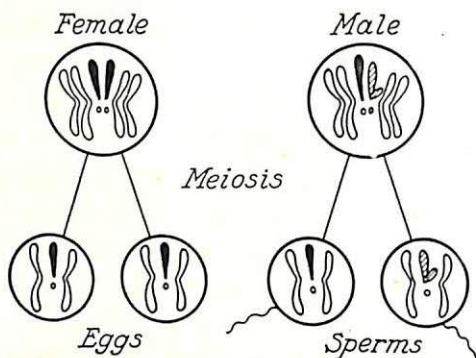


FIG. 40. Chromosomes of female and male *Drosophila melanogaster*, diploid; and of the haploid eggs and sperms. Note that the sperms are of two kinds, those with an X-chromosome and those with a Y-chromosome. X-chromosome, solid black; Y-chromosome, shaded; other chromosomes, outline.

taking part. Since all the eggs carry an X-chromosome, sperms carrying an X-chromosome will produce a zygote with two X-chromosomes. This will be a female. On the other hand, a sperm carrying a Y-chromosome will produce a zygote with an X- and a Y-chromosome, and such an individual will be a male (Fig. 41).

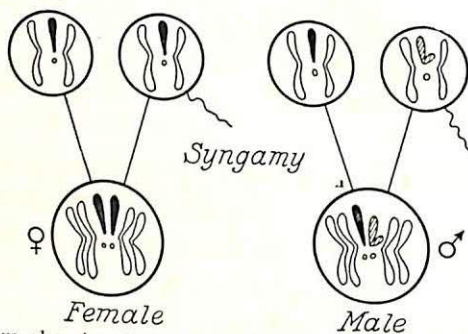


FIG. 41. Diagram showing how the male and female chromosomal constitutions are determined at syngamy by the kind of sperm taking part in fertilization.

In man, too, females have an XX- and males an XY-constitution. Here the X- and Y-chromosomes are not distinguishable by shape so much as by size. The Y is a great deal smaller than the X, and is, in fact, the smallest of all the

forty-eight chromosomes. Because we have so many chromosomes (and many of them are extremely tiny), trying to see and distinguish the X- and Y-chromosomes in a crowded nucleus is similar to hunting for a needle in a haystack. However, a number of cytologists have patiently sorted all the human chromosomes into pairs; and when these are arranged in parallel rows, one for the male and one for the female, the XY-pair in the male is obvious enough (Fig. 42).

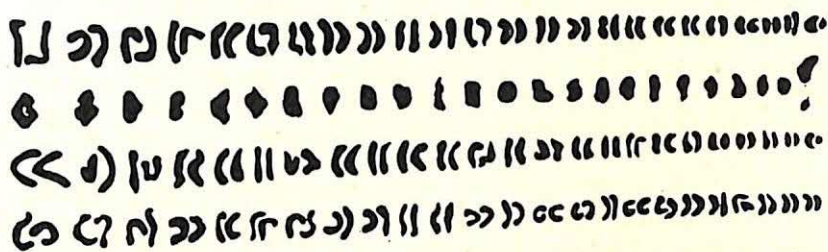


FIG. 42. The forty-eight human chromosomes paired and arranged in order of size. The three top rows are from male cells, the first row being from a cell of the germ line, the second row from a meiotic cell with homologous chromosomes in synapsis (hence there appears to be only the haploid number), the third row from a somatic cell. The X- and Y-chromosome pair is placed at the extreme right of each row, the Y-chromosome being the extremely small one. The bottom row is from a female somatic cell, no such unequal pair of chromosomes being evident. Magnified about 1600 diameters. (From Painter, after Evans and Swezy. Courtesy of the *Journal of Heredity*)

In the fruit fly the Y-chromosome, in comparison with the X, is fairly large, whereas in man it is very small. In some bugs, such as *Protenor*, unlike the type previously mentioned, it is lacking altogether. These female bugs have two large X's, but the males have only one. Sex, nevertheless, is determined in exactly the same way in these bugs as in fruit fly or man. Two kinds of sperms are formed, one kind carrying an X, the other lacking it, and hence having one less chromosome in all. At syngamy, $X + X$ yields a female; $X + O$, a male.

The determination of sex by a specific pair of chromosomes seems to parallel that which takes place in liverworts, but

the genetic situation is actually far different. First of all, in the higher animals the odd chromosome, or Y, which occurs only in one of the sexes, may be large or small or even entirely absent without any change in the nature of sex determination. This fact is itself suggestive. Perhaps the Y-chromosome has nothing to do with sex determination here!

We can test this idea by observing those occasional meiotic accidents when homologous chromosomes fail to disjoin. Such an accident, known as *nondisjunction*, may befall the X-chromosomes in the germ cells of a female, and would lead to two kinds of eggs. One would contain two X-chromosomes, the other none. In the normal course of events these would be fertilized by sperms carrying either an X- or a Y-chromosome. *Drosophila* again supplies us with the facts. The resulting types, as we can see from Fig. 43, are four in number. Neglecting for the moment the other chromo-

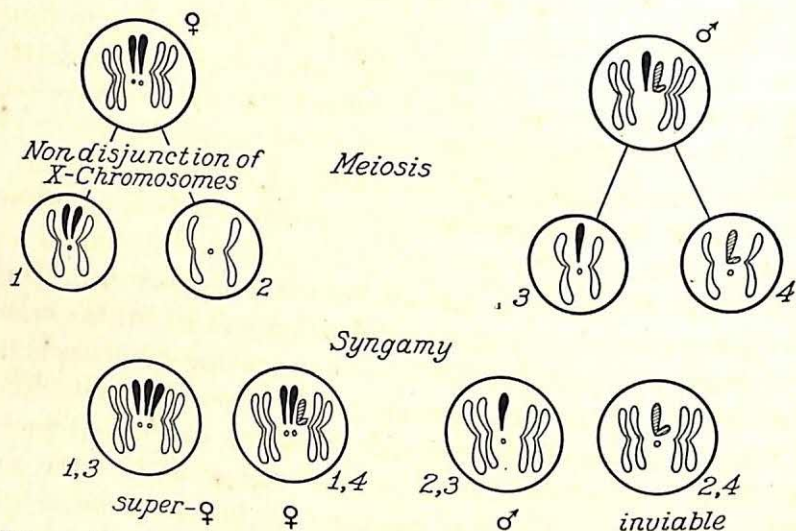


FIG. 43. The effects of nondisjunction in a female *Drosophila melanogaster*. Union of kind of egg No. 1 with kind of sperm No. 3 produces a three-X super-female, sterile; egg No. 1 with sperm No. 4 produces a normal female with an extra Y-chromosome; egg No. 2 with sperm No. 3 produces a normal-appearing, sterile male; egg No. 2 with sperm No. 4 yields a type without an X-chromosome that perishes early.

somes, all handed down quite as usual, we can describe these four types by their X- and Y-chromosome constitution. The first has three X's; the second, two X's and a Y; the third, one X; and the fourth, a Y. Now what sex have these combinations? Two, the second and third, turn out to be perfectly normal-seeming females and males. In other words, two X's and a Y have the same effect in determining sex as two X's alone, while a single X has the same effect as an X plus a Y. This amounts to saying that *the Y-chromosome has no sex-determining effect*. It is not truly a sex chromosome. *The X's are the sex chromosomes, two X's producing a female, one X a male.*⁹

These facts prove the responsibility of the X-chromosome for determining sex, but the question of the number of sex genes the X carries still remains. Many years of experiment and controversy elapsed before it was shown that there was no single major sex gene in the X-chromosome, but that numerous well-scattered genes in it act cumulatively in determining sex. This fact was demonstrated by a study of the effects upon sex of each one of a number of short successive segments of the X-chromosome, both in excess and in deficiency. Reliance upon many sex determinants rather than upon a single pair must frequently have proved itself good insurance against any disturbance of the system introduced by mutation. Combining this advantage with that providing for the segregation and recombination of an entire set of sex genes as a unit has achieved remarkable efficiency and durability for this, the prevalent mode of sex determination.

The sex genes of the X-chromosome are evidently female in effect. Where, then, in these diploid organisms with isolated sexes, such as the fly or man, are the male determinants?

⁹ The no-X type perishes while still an egg. It is unable to take even the first few steps in development. Flies with three X's do somewhat better, although none too well. If their environment is optimum in every respect, as many as half of them may succeed in passing the perils of pupation and in crawling out into adulthood, sterile weaklings with all sorts of defects. (They are called by geneticists *super-females*, but that certainly cannot mean a superior expression of feminine traits!)

Is the number of X-chromosomes the sole factor? Is a female just two doses of maleness? Or, turning it round, is a man, so to speak, but half a woman? This would be one way of explaining the situation just presented. A final experiment yields an answer.

Sometimes, though very rarely, of course, nondisjunction will involve, besides the sex chromosomes, all other pairs

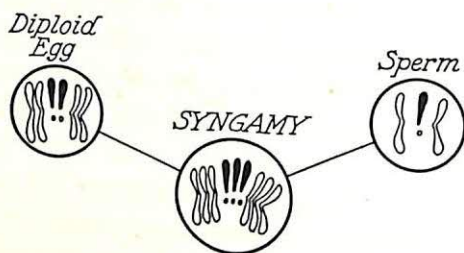


FIG. 44. The production of a triploid female through the union of a diploid egg and a haploid sperm (*Drosophila melanogaster*).

as well. In this way we may obtain an egg with a full diploid quota of chromosomes. Fertilized by an ordinary sperm carrying an X, an individual will arise with three of each kind of chromosome, a *triploid* (Fig. 44). Now this triploid is a perfectly vigorous, fertile *female*, although, like the super-female, it has three sex chromosomes. What is the difference? It can be only that the other chromosomes, the *autosomes*, as they are called, are triploid too. But this must mean that the autosomes, as well as the sex chromosomes, have to do with sex determination. To summarize, using A to stand for a haploid set of autosomes:

$$2X + 2A = \text{♀} \text{ and } 3X + 3A = \text{♀}; \text{ but}$$

$$X + 2A = \text{♂}, \text{ while } 3X + 2A = \text{super-female}.$$

This suggests that maleness and femaleness here depend on a particular *balance* or ratio between genes in the X-chromosome and opposing genes in the autosomes. Since, with a given set of autosomes, a cumulation of X's (from X to 2X) tends from maleness toward femaleness, we can say that *the*

sex genes of the X-chromosome tend toward femaleness, and those of the autosomes tend toward maleness.

This concept is further strengthened by observing what happens when a diploid egg, like the above, is fertilized by the type of sperm which carries a Y-chromosome instead of an X. The resulting individual would have two X-chromosomes (plus a Y), and three full sets of autosomes, that is, $2X + 3A$. If $3X + 3A$ is a female, we might expect $2X + 3A$ to be something less than a female; and, since the male ratio is $1X : 2A$, we might expect $2X + 3A$ to be something more than a male. This expectation is realized in fact. The $2X + 3A$ individuals are a peculiar type, with some characteristics of each sex. They are sterile *intersexes*. They usually resemble females somewhat more than males.

What an ingenious system is this that determines the sex of a diploid individual in spite of a multiplicity of sex genes, simply through the segregation of chromosomes at meiosis and their recombination at syngamy. One particular pair of chromosomes has become the sexual counterpoise of all the others; and this one particular pair has further become haploid in one sex and diploid in the other. Through segregation, individuals haploid for this chromosome produce two kinds of gametes; individuals diploid for it, only one. Hence there are produced at fertilization only two combinations, the female with two such chromosomes, the male with only one. In Fig. 45, this system is added to the more fundamental sex system, upon which it is superimposed.

In this way, then, sex is predetermined from the very instant of fertilization, along with the remainder of the hereditary pattern. Away with all superstitions that by thinking this or doing that we can determine the sex of our yet unborn children! What good to hope or dream or pray? Before growth and development ever commence, through the random chance of this or that sperm's arrival first at the egg, the genic combination is produced which will favor the expression of one of the two sexual potentialities.

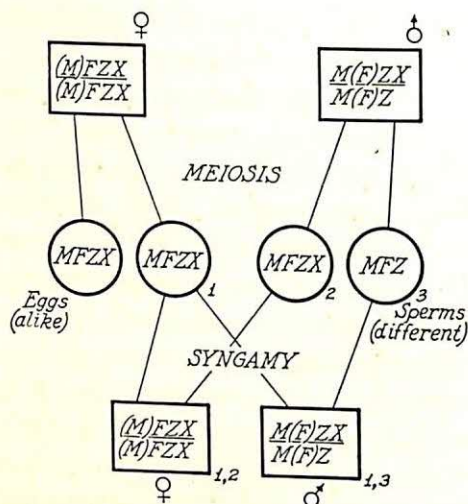


FIG. 45. Scheme showing the sex gene system of a form, like *Drosophila* or man, in which the male sex-determining genes (M) and some of the female sex-determining genes (F) are always homozygous, while other female sex-determining genes (X) are diploid in one sex, haploid in the other. The symbols for the sex genes whose effects are temporarily inhibited are placed in parentheses.

If we would ourselves control sex determination, we must first learn how to distinguish the two kinds of sperms and then how to separate them effectively. Although we may ultimately succeed—and there are those who claim to have detected a bimodal distribution of sperm size or weight—it remains as yet impossible to separate them.

Through the mechanism of meiosis, that is, through the segregation of X- and Y-chromosomes, female-producing sperms carrying an X, and male-producing sperms carrying a Y, are formed in equal numbers. A direct result is the numerical equality of the two sexes in a population. Birth statistics show us, however, that this equality of the sexes is only approximate. For every 100 girl babies born, there are on the average 105 boy babies. To what can this upset of the ratio be due? We think at once of the possibility of selective mortality during the prenatal period. Perhaps more girl babies die before or at birth. The doctors can tell us

something about this. "In the United Kingdom, the proportion of male to female deaths before birth is about 150 to 100; for still-births it is 135 to 100. . . . And just the same happens in other mammals, such as cattle." ¹⁰ Astonishing! Meiosis results in equal numbers of male-producing and female-producing sperms, more male embryos die before birth, more die at birth, and still there are 105 males to every 100 females. If we take these deaths into account, there must be about 120 males conceived to every 100 females. "This . . . can only be accounted for by some advantage possessed by Y-bearing sperms which enables them to fertilize more eggs than their X-bearing brethren. Presumably the male-producers have greater powers of endurance than the female-producers and can better withstand the arduous journey up the uterus and oviducts. We may guess from the statistics that for every six male-producers only five female-producers get to the top of the oviduct; that six out of every eleven among the millions that lose themselves and perish on the way are female-producers." ¹¹

Before passing on to quite another subject, one more word should be said about sex determination. The final type which we have just described is, indeed, that commonest among the higher animals, and it holds surpassing interest for us as the method whereby sex is determined in our own species; but it is after all only one of several. In describing the system, for example, it was said that one particular pair of chromosomes has become the sexual counterpoise of all the others. Now would it not seem as likely that this particular pair should carry the male-determining as the female-determining gene complex? If so, the situation would be quite reversed, XX producing a male, and XY (or XO) a

¹⁰ Wells, H. G., Huxley, Julian, and Wells, G. P. *The Science of Life*, p. 555. Doubleday, Doran, New York, 1931. Praise need scarcely be given to this comprehensive attempt to provide for the layman an understanding of the facts and values of biology. This quotation and the following speak for themselves, indicating both the individual and the social points of view developed, and the clear and appealing style.

¹¹ *Ibid.*, p. 557.

female.¹² The sperms would then all be alike, and the eggs would be of two sorts, destined to become either males or females. In the long evolution of animal life, this converse type of sex determination has arisen several times, for it is characteristic of two very unlike groups, the birds, and the moths and butterflies. It is also to be found in some of the fishes, where even closely related species differ as to which sex is heterogametic (XY, or XO).

Another change in the system, perhaps of a common sort, has been found in the gypsy moth (*Lymantria dispar*). In this species the sexual counterpoise to the determinants in the sex chromosomes has been located in either the Y-chromosome or the cytoplasm instead of in the autosomes.¹³ Since the egg alone contributes the Y and the cytoplasm to the offspring, this sex determinant, F, is transmitted through the female line, from mother to daughter. Numerous geographical races of this moth can be bred together, but then produce some intersexual offspring. These intersexes are not like those of *Drosophila*, which resulted from nondisjunction, for they have a normal diploid quota of chromosomes, and are either XX or XY in sex-chromosome make-up. Their intersexuality must therefore be due to a difference in the strengths of the sex determinants. Within any single race, M and F are so counterpoised that two M's and an F produce a male, but one M and an F produce a female. If the strengths of the M's (or F's) of two races fail to correspond, the delicate balance is disturbed in their offspring, and an intersex results. Even within this single species a number of M's and F's of differing strength have arisen, whether by mutation, by recombination, or by some other kind of change. It is quite likely that much of the sterility of interspecific hybrids has been produced in a sim-

¹² In order to avoid confusion with the type in which the male is the heterogametic sex, some geneticists prefer to use the symbols ZZ and ZW for XX and XY, when the female is heterogametic.

¹³ This raises the whole problem, which we have so far disregarded, of the existence of hereditary factors not located in the chromosomes. Very few are known, and these occur mostly among the plants. The topic can be treated better in Chap. IV.

ilar fashion, for in *Drosophila*, too, research has shown that numerous genes are responsible for the intersterility of two races of the same species (*D. pseudoöbscura*).

In the gypsy moth the evolution of the sex-determining mechanism appears to be still in progress. This evolution began with sexual bipotentiality; upon this foundation was superimposed the control of modifying genes, first, no doubt, simply haploid, meiotic; then came the more complex balance of male and female determinants and the appearance of the sex chromosomes, diploid in one sex, haploid in the other, which fix sex at syngamy, at the very beginning of the diploid phase of life. In the main line of evolution among animals the male has remained the heterogametic sex. But several times there has been a switch to the female, once in the evolution of the insects, one or more times in that of the modern bony fishes, and again at the time when birds diverged from the ancestral reptilian stock. Within each isolated population, alterations in the sexual mechanism have taken place so that interbreeding with related populations, whenever the isolation breaks down, is more and more restricted. Sexual isolation adds its effect to other forms of isolation, and the incipient species diverge more than ever. This we can see still going on in modern organisms, for the evolution of sex is not ended. Had it been possible for some human race, such as the Pygmies of Central Africa, to maintain its isolation a few thousands of generations longer, we might perhaps have seen it shut off from us forever through barriers of intersterility more potent than those of ocean, desert, and jungle.

GENES CARRIED IN THE SEX CHROMOSOMES ARE INHERITED
IN AN EXCEPTIONAL "SEX-LINKED" FASHION

The sexual mechanism prevalent among the higher animals has important consequences in the hereditary pattern, consequences we should not overlook. These result from the

inheritance of genes, other than those affecting sex, in the sex chromosomes—and we may include the Y-chromosome, too.

Genes in the X-chromosome are “sex-linked.” This does not mean that they are limited to a particular sex, but that they follow the X in its distribution. This is not their only peculiarity. There is another, a unique thing to be taken into consideration.

Most of the genes in the X-chromosome have no alleles in the Y-chromosome. In fact, if we may generalize from what we know is true in the fruit fly, there are very few genes of any sort in the Y-chromosome. It is little more than a dummy! The genes in the X-chromosome of the XY male are consequently haploid, and dominants and recessives alike will exert their effect without modification by alleles.

Although our X-chromosomes are by no means the largest we have (they come about two thirds of the way down the scale of size among our twenty-four pairs; see Fig. 42), more human genes have been detected in the X than in all the rest combined. This, of course, is not because the X has more genes, but because its haploid condition in males and the unique character of its transmission make detection a great deal easier than for autosomal genes. Of the more than twenty available examples, the best known are red-green color blindness and hemophilia. Although hemophilia has been more widely publicized because of its notorious presence in the former royal houses of Bourbon in Spain and Romanoff in Russia,¹⁴ it affords a poor example, since no definite cases of affected women have ever been reported, probably because the female environment prevents its appearance. The more typical behavior of color blindness will, therefore, serve us better (Figs. 46, 47).

¹⁴ It was through the desperate efforts of the Czarina to find some form of relief for the chronic bleeding of her son, the Czarevitch, that Rasputin came into power. His evil influence was a factor of importance in the outbreak of the Russian Revolution. Thus the gene for hemophilia has considerable historical importance!

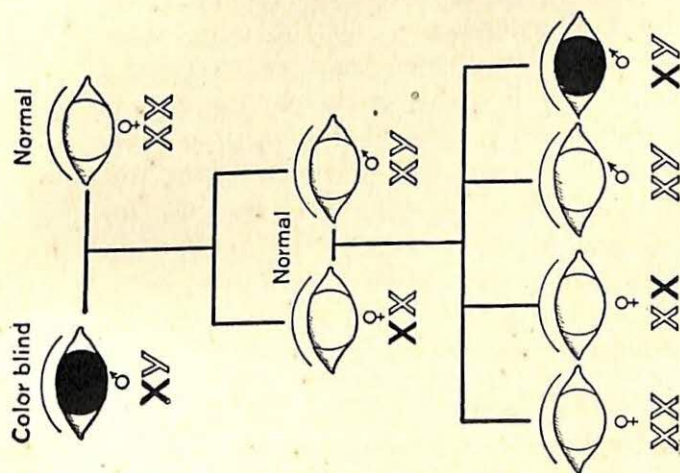


FIG. 46

FIG. 46. The inheritance of color blindness. A color-blind male mated with a normal female. The color-blind male transmits this defect through his daughters only and it appears only in his grandsons, since their Y-chromosomes contain no dominant normal gene to hide their X-chromosome gene for color blindness. The inheritance of this character discloses the distribution of the X- or sex, chromosome to the gametes and progeny. X-chromosomes carrying the gene for color blindness are shown in black. (From Dunn's *Heredity and Variation*. Courtesy of The University Society, New York)

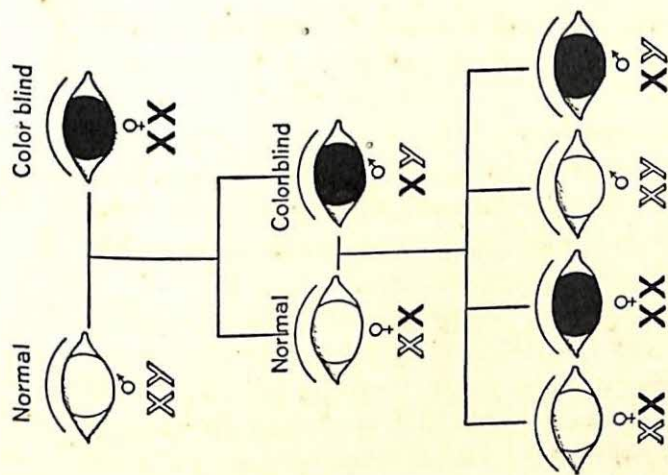


FIG. 47

FIG. 47. The inheritance of color blindness. A normal male mated with a color-blind female. The color-blind female transmits her defect through her sex (X) chromosomes to both sons and daughters. The defect appears only in the sons because the daughters receive a normal (dominant) gene in the X-chromosome from their father, while the Y-chromosome does not carry the normal gene. (From Dunn's *Heredity and Variation*. Courtesy of The University Society, New York)

"A color-blind male transmits his defect only to his grandsons through his daughters, never to his sons, but a color-blind mother, even though her husband is of normal vision, always transmits her defect to all her sons. This is precisely the mode of transmission of the X chromosome in man, and a sex-determining X chromosome bearing the genes for these traits had to be assumed to explain this type of heredity even before it was discovered under the microscope."¹⁵

Drosophila has at least one gene located in its Y-chromosome, and it is possible that a few of our genes, too, are located in this minuscule chromosome. This raises an interesting question. How would such genes be inherited? Would they form a completely independent, though small, linkage group limited to the male? Or do genes in the Y-chromosome have alleles in the X with which they can, at least occasionally, exchange places? For, though most of the genes of the X have no alleles in the Y, this is no assurance that the few genes of the Y might not have alleles in the X-chromosome. The situation was long assumed to be the former, and several examples of "sex-limited" inheritance were attributed to location of the responsible genes in the Y-chromosome. Sex-limited traits in vertebrates are, however, brought about by another means, and more careful investigation of the best-known case, the "bobbed-bristle" gene of the fruit fly, has shown that it, indeed, has an allele in the X, and that it crosses over with it occasionally. In fact, it is now clear that almost one half of the X-chromosome of *Drosophila* is, like the Y, practically empty of genes, and the allele of the bobbed-bristle gene lies in this portion.¹⁶ The main gene-containing part is stuck on to this "empty" portion as an ap-

¹⁵ Dunn, L. C. *Heredity and Variation*, p. 72. University Society, New York, 1934. This short book is by far the best treatment of the subject for the lay reader which has yet appeared. It succeeds eminently in being readable, in avoiding unnecessary technicalities, and in dealing with the major values of an understanding of genetics.

¹⁶ The Y-chromosome of the fruit fly also carries two separate "factors" (whether or not they are comparable to other genes cannot be said) which are essential to the fertility of the male.

pendage. The true relation between the X- and Y-chromosomes is that of a potent sex-determining fragment, carrying also many other genes, attached to one of a pair of singularly empty chromosomes (Fig. 48). This explains why the appar-

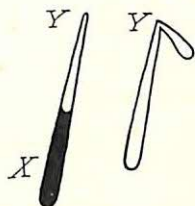


FIG. 48. Diagram showing (in white) the portion of the X-chromosome of *Drosophila* that is homologous to the Y-chromosome. The normal Y is to the right.

ently dissimilar X and Y act as a pair and regularly segregate in meiosis. Recently a new significance has been attached to the Y and various other parts of certain chromosomes *which seem to be empty of genes*. Although these parts of the chromosomes do not carry genes like the rest, nevertheless, their importance may be considerable. For we now know that the action of many genes, their dominance, or their mode of expression may be modified by their position with respect to such "inert" material within the same chromosome.

This is by no means the whole story of the development and significance of sex, but its place in the hereditary pattern of an individual at life's outset is sufficiently clear without further discussion. The grand cycle of meiosis and syngamy redistributes the mutations of the ancestors in ever varying combinations, some good, some not so good, to their offspring; and through natural selection they are then weeded out. Thus is produced the fitness of life-forms for their environment. Thus, too, through constantly arising mutations there enters each stock a flow of new variation through which is preserved that adaptability of life-forms so essential to survival in a changing world. All this is the matter of evolution,

which would require another book to treat as fully as it deserves.

Through the situation of the genes in organized bodies, the chromosomes, which form the basic units of meiosis and syngamy, there arises the inheritance of traits in groups, the phenomenon of linkage. And, through crossing over, the limitations set by linkage upon variety in hereditary pattern are overcome, the unit in the pattern becomes the individual gene instead of the chromosome, and the possibilities of recombination soar into the infinite.

Finally, there is the phenomenon of sex determination, with its secondary effects, such as sex-linked inheritance. Basic is the sexual bipotentiality of every cell and organism. Superimposed upon this is genic control of the time of sex determination, bringing as its by-product—significantly for us—the isolation of the sexes. Last comes sex determination for the diploid organism achieved potentially by segregation and realized at the moment of syngamy—the balance of sex genes inclining one way toward femaleness, the other toward maleness.

How sex is realized is a part of the story of development, which we are now ready to survey. During development the various features of the environment may even, in the lower animals, play so profound a part that the predetermined sex is overruled and completely reversed. This is true not only of sex but also of every other element of the hereditary pattern. The expression of each gene or gene complex is utterly dependent upon the environment. Our hereditary pattern is in a sense only the accumulated hereditary control of our race over certain features of our environment. That control is far from complete or perfect. Development is the constant interplay of our genes and our environment; we ourselves are the arena in which the contest is played to its close.

CHAPTER IV

The Basis of Growth and Development

LIKE all life-processes, growth and development consist essentially of controlled chemical and physical transformations of matter. This is really but another way of stating our fundamental axiom that all the characteristics of an organism are produced by the interaction of its heredity and its environment—that the two can never be divorced. For the controls of these processes are such that every organism resembles its parents, and in this lies heredity; while the chemical and physical transformations of matter can take place only where conditions are appropriate—and this is the action of the environment.

Even the autocatalysis of the genes cannot occur except where raw materials and energy are supplied. The cytoplasm of the cell represents their necessary environment. Nor can a human cell live successfully apart from the balanced environment of the body, with its checks and controls against sudden or extreme fluctuations of a chemical or physical character—unless in a skillfully simulated duplication of it. As development proceeds, our cells acquire different forms and become suited to carry on different types of work, *according to their situation and relations to the rest of the organism and the outer world, but also according to their own innate capacities.* Life and environment are no more separable on this level of existence than on any higher plane.¹

¹ See Sears, P. B. *Life and Environment*. Bureau of Publications, Teachers College, Columbia University, New York, 1939.

A certain breed of rabbits lays up white fat on a diet of mash and potatoes, yellow fat on a diet of mash with green-stuffs. But most rabbits lay up white fat on either kind of diet. Considering only the first kind of rabbit, the variation in environment seems to be the decisive factor. But with both kinds of rabbits fed on green food it is the genetic constitution that obviously makes the difference. We can appreciate the effects of heredity on the one hand, and environment on the other, only when we isolate one through neutralizing the effect of the other, that is, when we render it constant. Heretofore we have discussed the effects of heredity while assuming that environment was constant. In Chapter V we shall do the opposite. For the present, we must try to relate the two to each other.

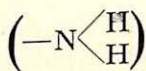
Growth and development involve the absorption and assimilation of materials. This is mainly water, for the bulk of all protoplasm—two thirds of the body weight in man—consists of water. But the characteristic sizes, shapes, and types of organization assumed by developing organisms are obviously not a simple matter of the imbibition of water or the absorption of other simple substances, such as salts, however essential these may be. Growth and development involve an increase in volume and a change in character of a colloidal protein system. It consists to a large extent of chemical syntheses. The controlled chemical transformations of matter that underlie growth and development differ markedly from those involved in other primary metabolic processes, such as hydrolysis, oxidation, and fermentation. The latter are destructive and energy-releasing, while the former are constructive and hence consume energy.²

The materials for these syntheses are the products of digestion, mainly those of protein digestion, the amino acids. It is true, of course, that both carbohydrates and fats are synthesized in our bodies, too; yet this is merely laying up a

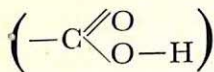
² This contrast is what the biologist has in mind when he divides metabolism into *catabolic* and *anabolic* phases.

reserve food supply, and consists principally of producing insoluble foodstuffs from soluble ones. Aside from water, the great mass of the living matter, the protoplasm itself, is mainly protein, along with various complex phospholipins and sterols. The syntheses of proteins are substantially similar to those of fats and carbohydrates, for all represent a reversal of the hydrolysis which splits larger molecules into smaller ones during digestion. The splitting action of water molecules (H-O-H) depends upon the addition of a hydrogen atom to one portion of the molecule to be digested, and a hydroxyl (OH) group to the other, with a consequent separation at the connecting bond. Conversely, *synthesis mainly involves dehydration*. A hydrogen atom from one amino acid unit and a hydroxyl group from another are removed to make a molecule of water, and the units are bonded together at the points of loss.

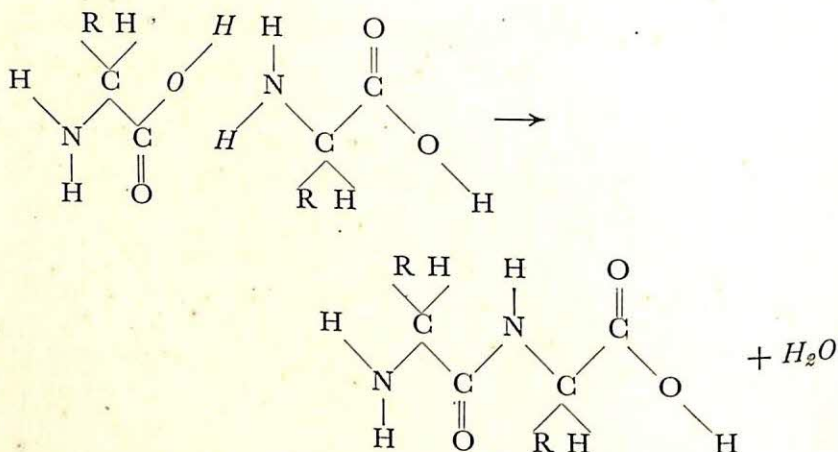
The distinguishing characteristic of an amino acid is the presence of both an amino group



and an organic acid (carboxyl) group



in the molecule. The dehydration synthesis of proteins from amino acids proceeds through a loss of a hydrogen atom from the amino group and a loss of a hydroxyl group from the acid group (these combine to make water), and a resultant bonding of the amino and acid groups of the two units. This we can diagram simply, if we let R stand for the bulk of each amino acid. The hydrogen atom and hydroxyl group that come out and the water they combine to make are each italicized for identification. Then:



The double group thus obtained still has an amino group on one end and an acid group on the other. This enables it, like any simple amino acid, to enter into further combinations, until finally thousands and tens of thousands of such units may be combined into the huge protein groupings.

Hydrolysis releases energy, but in very small amounts compared with those obtainable from oxidations or even from fermentations. The converse synthesis requires energy, but only to a corresponding degree. *Growth is consequently a very economical process, one which consumes but little of our available energy.* The limiting factor in the growth of malnourished and half-starved individuals is to be found in the lack of particular foodstuffs which are essential for certain syntheses rather than in a generally inadequate supply of energy. This is a consideration of very great value in indicating the direction we should take in planning the satisfactory diet.

Water, to be sure, will neither split large molecules nor bond smaller ones into larger, unless the reaction is catalyzed. Whether we are digesting or, conversely, synthesizing new proteins, enzymes are required; and presumably the characteristic nature of human proteins, the product of the syn-

theses, is due to the specificity of the enzymes controlling them. Let us, for example, imagine ourselves sitting down to a sizzling beefsteak. It is composed of proteins of specific kinds, recognizable as definite beef proteins. We eat our steak, digest it step by step into its component amino acids. It is then absorbed and carried by the blood to our cells. Here begins the task of synthesis. Proteins are to be reconstructed from these amino acids. Enzymes for the dehydration syntheses are produced, and unit by unit the proteins are built up. When all is complete, however, the proteins are not *beef* proteins, but characteristic *human* proteins. Here are the same units, but combined in different proportions, in different arrangements! We might go so far as to say that we differ from the cow because we have different proteins.

Different proteins in turn imply different synthetic patterns, controlled by different enzymes and precursors. Now why should human cells produce distinctively human groups of enzymes and beef cells distinctively beef groups of enzymes? The distinction is clearly a hereditary one. Parents produce offspring of their own kind because mitosis ensures a lineal descent of genes. The action of the genes must constitute a control over the cytoplasmic production of enzymes and the simpler constituents which are the precursors of the ultimate products.

Growth and development primarily involve *specific chemical syntheses*, which depend on *specific enzymes and precursors*, which in turn depend on *characteristic genes*, which are *inherited*. We need, then, to learn how genes interact with one another, and how they control the production of secondary substances, if we are to arrive at an understanding of this aspect of life. Growth and development are secondarily matters of differentiation within an individual, the appearance of distinctive form and structure through the specialization of cells, the emergence of a "division of labor." This chapter

is, therefore, divided into two main sections, the first of which deals with gene and enzyme interactions.

GENES INTERACT TO PRODUCE TRAITS

In Chapter II there was described a certain kind of gene interaction, that of alleles. These, we learned, may blend in their effects, or one allele may completely dominate the other, recessive allele. All too common, however, is the misconception which *limits* gene interaction to alleles. On the contrary, many, if not most, genes affect a variety of traits, and there need be little reserve in asserting that *all traits are the product of the interaction of a number of genes.*

Most genes produce a number of effects

We have taken the gene which is responsible for albinism as our example a number of times. It may serve again. In the first place, it is not limited in its effect to an absence of pigment in the superficial layers of the body. It has also a pronounced effect upon the disposition, at least in mice, rats, and rabbits. "White" rats, mice, and rabbits are far gentler than their pigmented relatives, even when sibs of the same litter. That is why they are generally preferred as pets. An albino rat is mild and curious. It can be held in the hand, and likes to explore sleeves and pockets. A normally pigmented gray rat can hardly be handled so boldly. Only patient training will curb its readiness to bite.

This is a single example. There is also proof that the multiple effect of genes is rather general. It comes from the study of deficiencies, of losses of pieces from a chromosome. Many of these losses are so small that they involve, in all likelihood, only a single gene.³ Yet there are relatively few deficiencies which are not lethal when homozygous in the individual.

³ In *Drosophila*, the extent of these deficiencies can be studied in the giant salivary gland chromosomes. Many represent losses of only a single cross-band (see Fig. 3), and the number of these corresponds closely to the total number of genes, as estimated in other ways.

Most of them, in fact, are lethal even to single homozygous cells, though these cells may be surrounded by viable (heterozygous) tissues. These facts point to actions of the genes far more vital than any mere alteration of pigment or determination of hair or bristle form. *Most genes are essential to the life-processes of each individual cell.* The effects we commonly observe are only superficial.

Most traits involve the interaction of a number of genes

The difference between our two common eye colors, brown and blue, is due to a single pair of alleles (B, b). The heterozygous combination, B/b , is a blend, variously known as gray or hazel, with the brown usually predominating over the blue. But eye color is not solely determined by this pair of genes. We have already learned that when the genotype of an individual is homozygous for the "albino" gene (a), there is no pigment in the iris of the eye, and the red of the hemoglobin in the blood makes it appear pink. In an albino the genotype must include the other pair of genes, too, for all pairs are normally represented, but here this second pair fails to produce any effect. If, however, the genotype, as respects the albino gene, is A/A or A/a , then the eye color is fixed by the genotype of the second pair, B/B , B/b , or b/b . Why is this?

If we consider the chain of chemical syntheses leading up to the final production of pigment in the eye, it will become clear that the genes which control earlier steps in the chain will exert such influence that they may alter or nullify the action of genes controlling later steps. They possess a marked precedence (*epistasis*) over them. In fact, just as we may shape and bake a lump of dough in various ways, but without dough can bake no bread, so here the genes producing brown or blue color in the iris only alter a substance already provided, and in its absence can do nothing. Figure 49 is a simple diagram to illustrate the situation.

This by no means completely describes the situation. The hazel phenotype is extremely variable (gray, green, violet, apparent brown), and this in turn rests upon the action of still other gene pairs, so-called "modifiers."⁴

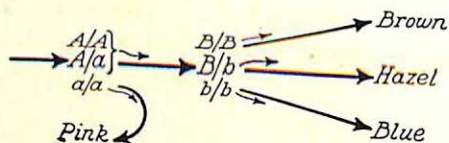


FIG. 49. The heavy arrows represent alternatives in the chain of chemical reactions concerned in the production of eye pigment. Alternative genotypes are placed above one another at a specific point in the chain-reaction, and the small arrows indicate respectively the direction taken by the chain-reaction for each genotype.

Another possibility is that two or more pairs of genes may affect the same stage in the chain of reactions leading to the expression of a trait. An example lies close at hand. We can find it in another end-reaction of this same chain, that which produces pigment in the skin. The early part of the chain is the same. (As a matter of fact, one frequent sign that a gene pair precedes others in its action is the wider extent of its effect within the organism. Thus the nonalbino-albino pair of genes is body-wide in its effect, while the later-acting genes

⁴ A mating between individuals, each heterozygous for both of these pairs of genes ($A/a; B/b$), will result in a modification of the typical $9 : 3 : 3 : 1$ phenotypic ratio expected from a dihybrid cross. It will assume the form $9 : 3 : 4$, since the entire one fourth of the progeny having the genotype a/a will be albino, regardless of the genotype of the other pair. Whenever the dominant of a primary pair, rather than the recessive, inhibits the expression of the secondary pair (we may visualize this by switching the positions of a/a and $\begin{Bmatrix} A/A \\ A/a \end{Bmatrix}$ in Fig. 49), then the ratio becomes $12 : 3 : 1$. Such, in dogs, is the interaction of a primary pair (no pigment in hair versus pigment) with a secondary pair (black versus brown), which gives an F_2 ratio of 12 white : 3 black : 1 brown. Moreover, a pair itself like the nonalbino-albino pair may be subject to the precedence of a dominant inhibitor. In the White Silkie breed it is due to a recessive. In the F_2 from a cross between a variety of results.

are limited in expression to a portion of the organism, such as the eye, or the skin.) The final reaction appears to be catalyzed by two pairs of genes, the alleles in each of which blend, while each pair is exactly comparable in effect to the other. We may denote the genes producing heavy deposits of melanin as S and T , and their respective alleles, which produce only slight deposits, as s and t ; and then diagram as before (Fig. 50):

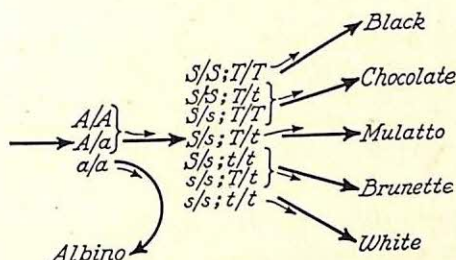
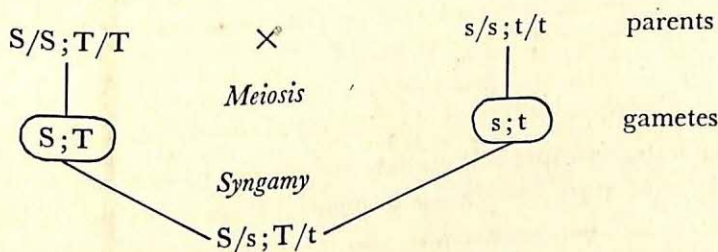
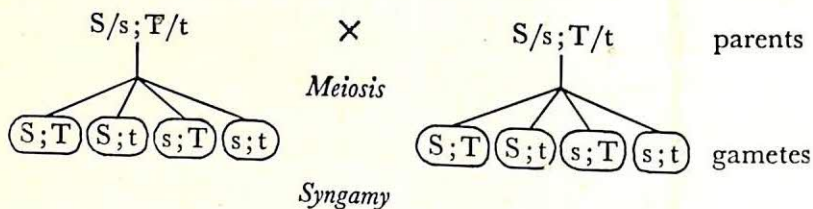


FIG. 50. The chain-reaction leading to the production of skin pigment. See Fig. 49.

As a consequence of the type of interaction we find here, it follows that a mating of black and white will always produce mulattoes, a very uniform class; for:



A mating between mulattoes of this genotype results in a way surprising to most of us, in fact, quite confounding many of our preconceived opinions, as the following diagram shows:



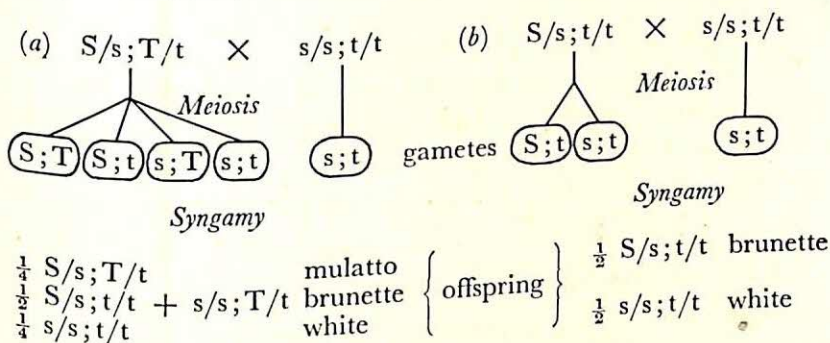
	$S;T$	$S;t$	$s;T$	$s;t$	
$S;T$	$\frac{S}{S}; \frac{T}{T}$ B	$\frac{S}{S}; \frac{t}{T}$ C	$\frac{s}{S}; \frac{T}{T}$ C	$\frac{s}{S}; \frac{t}{T}$ M	
$S;t$	$\frac{S}{S}; \frac{T}{t}$ C	$\frac{S}{S}; \frac{t}{t}$ M	$\frac{s}{S}; \frac{T}{t}$ M	$\frac{s}{S}; \frac{t}{t}$ Br	Black (B) —1
$s;T$	$\frac{S}{s}; \frac{T}{T}$ C	$\frac{S}{s}; \frac{t}{T}$ M	$\frac{s}{s}; \frac{T}{T}$ M	$\frac{s}{s}; \frac{t}{T}$ Br	Chocolate (C) —4
$s;t$	$\frac{S}{s}; \frac{T}{t}$ M	$\frac{S}{s}; \frac{t}{t}$ Br	$\frac{s}{s}; \frac{T}{t}$ Br	$\frac{s}{s}; \frac{t}{t}$ W	Mulatto (M) —6
					Brunette (Br) —4
					White (W) —1

Mulattoes may have completely black or completely white children! In fact, the expectation for either of these is quite high, 1 in 16.⁵ Moreover, these extreme types are both homozygous, and, therefore, not only appear pure black and pure white, but will breed as pure black or pure white, respectively. What a far cry this is from the common belief that racial intermixture permanently contaminates the heritage of every descendant! With this example we begin to see what Mendel's first principle really signifies. Because heredity is due to units, genes, which segregate and recombine generation after generation without themselves being affected, it must follow that segregants such as these pure whites and pure blacks will emerge from hybrid matings.

⁵ This is according to Davenport, who has studied the matter most thoroughly. Some other geneticists are inclined to think that more than two pairs of cumulative factors are concerned in skin pigment and hence that the expectation for pure black or pure white children of mulattoes is not more than 1 in 64. On the other hand, matings of whites with half-caste Bantu negroids in South Africa frequently produce children with white skins, blue eyes, and straight yellow hair. The difference in skin color may here depend upon only a single pair of genes.

These segregants, insofar as these two particular pairs of genes are concerned, inherit from only two of their four grandparents.

In our own country, a large part of the racial intermixture going on comes from matings of white with brunette or mulatto types. This, in contrast to mulatto by mulatto matings, results in a greater proportion of white segregants and an increase in the brunettes, who are frequently light enough to pass as white, and often do.



The gradual infusion of white "blood" into our American Negro stock is, of course, recognized by everyone, but not everyone has been equally ready to see the impracticability of treating the pure white segregants of hybridization as blacks. A more poignant expression of the problem is to be found in the personal difficulties of the pure white segregants who are reared in mulatto families.⁶

It is, of course, true that there are other negroid traits besides blackness of skin, yet these are few in number. There is a dominant gene for kinky hair, and a pair or two for facial features. In all, it is unlikely that there are many more than six pairs of genes in which the white race differs characteristically, in the lay sense, from the black. Whites or blacks, however, unquestionably often differ among themselves by a larger number than this, a fact which reveals our

⁶ These were excellently portrayed in the movie, "Imitation of Life," which appeared in 1935.

racial prejudices as biologically absurd. It is only the consistency of the difference, not its magnitude, which looms so large in our eyes. Differences between other races are probably even less, and those between such sub-racial groups as "Nordics" and "Mediterraneans" are negligible. *The chasm between human races and peoples, where it exists, is psychological and sociological; it is not genetic!*

The interaction of gene pairs in the manner just illustrated by those for skin color may be called *cumulative*, since the alleles of the two pairs are equivalent in effect and additive in action. A slightly different cumulative result obtains whenever the alleles in each pair are dominant and recessive. In Duroc-Jersey hogs, for example, the typical red color results from an additive effect of two dominants, each belonging to a different pair, and either alone producing a sandy color, while the double recessive is white. By referring to the checkerboard diagram (p. 172), we can figure out that there would be an F_2 ratio of 9 red : 6 sandy : 1 white.

Somewhat more frequent are instances in which the dominants produce an equivalent, but not an additive, effect. Thus they are duplicates of one another, and only $1/16$ of the F_2 progeny will express the recessive trait; that is, the expected ratio is 15 : 1. Feathered shanks in poultry and the typical triangular, rather than ovoid, seed capsules of the world's most widely distributed weed, shepherd's purse (*Bursa*), are inherited as just such duplicate dominants.

Finally, there are instances in which either dominant alone is ineffective, and the trait is produced only by their interaction. Normal hearing in man appears to be of this class, judging from a number of pedigrees; while the contrasting trait, deaf-mutism, is the consequence of the absence of either dominant allele (D or E). Two deaf-mute parents may thus have all deaf-mute children, or no deaf-mute children, depending upon whether their own deafness is due to the absence of the same dominant, or of different dominants, respectively (1) $D/D;e/e \times D/D;e/e$ and (2) $D/D;e/e \times d/d;E/E$.

This could not be the case were deaf-mutism due to either a dominant or a recessive single gene. Many other examples of this type are known, especially among plants. The 9 : 7 ratio⁷ which is produced in the F_2 by such a "complementary" interaction was first discovered in the flower color of the sweet pea, in the early days of genetics (1900-1910). The characteristic purple color of the petals comes from a pigment (an anthocyanin) which is synthesized from two components. Each of the dominant alleles of the two pairs of genes concerned is essential for the production of a particular one of these components.⁸

*Quantitative variation, insofar as it is genetic,
depends upon the cumulative action
of multiple factors*

A moment's reflection, and we can see that the traits we have hitherto used as examples are qualitative; they are not continuous variations, like height or weight, along a quantitative scale. Yet we worry principally over the latter sort when we wonder about our *normality*. Are we too tall or too short? Are we too fat or too thin; overweight or underweight; healthy or sickly; intelligent or stupid? These characteristics are extreme variants in continuous distributions which have an average. Are we sufficiently near this average to be normal? Perhaps all of us have at some time doubted.

A rude indication of continuous quantitative variation is, nevertheless, already apparent in the example which showed how two pairs of genes act cumulatively to determine skin pigmentation; indeed, we may even discern it in simple blend-

⁷ That is, 9/16 of the offspring will carry both dominants; 3/16 will carry the first dominant but not the second; another 3/16 will be just the reverse; the first dominant or with none is 7/16. (See checkerboard diagram, p. 172.)

⁸ The "throwbacks" and "reversions" of the breeders may be due merely to the homozygous reappearance of a recessive trait. On the other hand, they are probably more often examples of the reunion in one individual of complementary factors long isolated in different stocks.

ing, as in the pink four o'clocks, for example. For, if we diagram the relative frequencies of the various classes, we obtain a figure highest in the middle and falling off symmetrically on either side—that is, with the most abundant class the intermediate one (Figs. 51, 52).

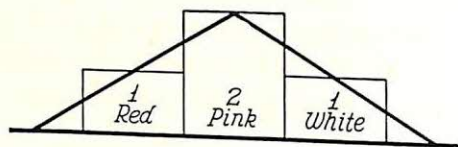


FIG. 51. Block diagram and frequency curve to illustrate the quantitative distribution of phenotypes in the F_2 generation from the cross of red by white four o'clocks.

In Figs. 51 and 52 the area above each unit along the base line represents the relative frequency of the respective class. These block-shaped figures may also be expressed in the form of curves superimposed by connecting the midpoints of adjoining classes, and this makes it easier to compare the distributions at a glance.

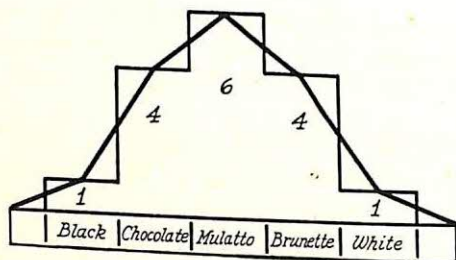


FIG. 52. Block diagram and frequency curve to illustrate the frequency of the various phenotypes among the offspring of mulattoes.

Were we to plot the results in the F_2 generation from a hybrid mating involving *three* pairs interacting in this same cumulative fashion, we would get phenotypic classes in the ratio 1 : 6 : 15 : 20 : 15 : 6 : 1. A mathematician would quickly see that each of these three ratios is an expansion of the expression $(a + b)^n$, where n is, respectively, 2, 4, and 6.

(This is known as the *Binomial Expression*, and its expansion to any power forms a *binomial distribution*.) Once we realize that these ratios are all expansions of the same simple expression to various powers, we can calculate the binomial distribution—in other words, the phenotypic ratio—for any number of pairs of interacting genes. If we do this, we find that as n increases—as more and more pairs of genes are concerned—our distribution approximates ever more closely the bell-shaped curve in Fig. 53. This curve, therefore, expresses

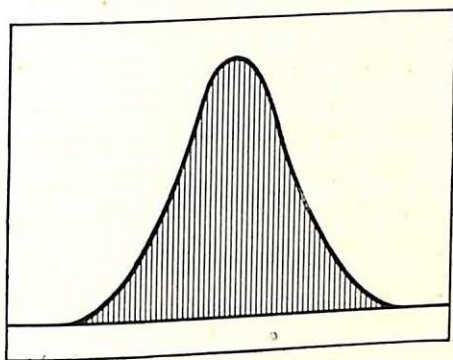


FIG. 53. The normal frequency curve derived from the expansion of $(a + b)^{20}$, corresponding to the frequency distribution of a characteristic determined by twenty pairs of interacting genes.

the normal probability of inheriting any degree of a quantitative trait determined by a great many genes.

The normal frequency curve expresses graphically and concisely what is really meant by "being normal." Only a frequency distribution itself can truly be normal. Wherever we set limits, on either side of the distribution's mean,⁹ limits within which lie the "normal" and beyond which the "abnormal" commences, we are necessarily arbitrary. For, whether the variation in the distribution is due to the ran-

⁹ The mean is the commonly used arithmetical "average." It is found by adding the scores (or measures) of the individuals in a distribution, and dividing by their number. If the individuals are grouped into classes, the mean becomes $\Sigma fV/n$, where Σ stands for summation, f is a class frequency and V its value, n being the total number of individuals.

dom segregation and recombination of many pairs of genes, or to chance environmental factors, or, as is most likely, to both, in any case the extreme deviations from the average are normally to be expected in their due proportions. It is no more just to speak of an extremely tall or extremely stupid person as abnormal than it is to think of brown skin as normal and black skin or white skin as abnormal. The latter are simply extremes in a rather discontinuous distribution, while tallness and shortness, morosity and genius, are extremes in continuous ones.

Nevertheless, there are individuals who appear to lie entirely outside the continuous normal distribution—a person nine feet tall or one weighing 450 pounds. There are groups, too, which seem to form secondary normal frequency distributions alongside the major one, so that a bimodal¹⁰ curve is produced. There are, for instance, the midgets in the height distribution and the imbeciles, idiots, and feeble-minded in that for intelligence. Here we meet a discontinuity which is due to the effect of some preponderant factor, genetic or environmental, acting differentially in the major and secondary groups. When two such distributions overlap, it becomes impossible to say offhand to which one any particular individual from the overlapping region belongs. Is Jeff a tall midget or merely a short man? Only a careful study of his family pedigree, childhood diet, and health record may enlighten us as to which of two normal distributions, the midget or the "normal," he belongs.

Whenever the differential factor acts infrequently, the rare affected individuals either stand alone or are unrecognizably merged with the extremes of the normal distribution. Here we cannot help but be arbitrary. Yet we can at least set the limits of the normal distribution so that there is but a negligible chance that anyone falling outside them is actually an

¹⁰ The mode of a distribution is simply the point (or class) of highest frequency. When a distribution has two such "peaks," separated by a "valley," it is said to be bimodal.

extreme variant of the major group. Even the most extreme 5 per cent of the distribution is not a negligible portion, for, with respect to each quantitative trait, one individual in every twenty would on this basis be classed as "abnormal." Scientists, with customary caution, usually set the thresholds of significant, that is, of *non-random*, deviation from the average where only 0.13 per cent of the distribution lies beyond them at each extreme.¹¹ This means that only one individual in 400 will be erroneously regarded as "abnormal" when he is really only an extreme variant of the random variation characteristic of the group.

When individuals of the second generation from any cross between extremes which differ because of "multiple factors" are bred together, there is a slight but definite probability that any single one of the offspring will be as extreme as either parent. There is an overwhelmingly greater likelihood that an individual will be intermediate—"average." Now within large mixed populations such as ours, most individuals will be heterozygous for the majority of whatever multiple factors are involved. That is, most of us are like the first-generation offspring of extremes. For this reason we can expect the children of average couples among us to correspond to the probabilities of the curve for all such traits as height, weight, mentality, general vigor, and resistance to disease, insofar as these are inherited.

¹¹ This proportion of the area of the normal curve is determined from the standard way of measuring the variability of a normal distribution, by calculating the standard deviation (σ). This is the square root of the sum (Σ) of the squares of all (f) deviations (d) from the mean, divided by the number of individuals (n) in the distribution ($\sigma = \sqrt{\frac{\Sigma fd^2}{n}}$). The standard deviation, when laid off on both sides of the mean, includes 68.26 per cent of the area of the normal curve, and $\pm 3\sigma$ includes 99.74 per cent of the area; that is, all but 0.26 per cent. Here we have one of the most valuable of all statistical measures to the scientist, who is constantly wanting to know whether a certain difference he observes is probably due to chance or has other significance. To be sure, the choice of $\pm 3\sigma$ as the criterion of significance is arbitrary—but it is *conservative* and *consistent*. The trouble with most of our judgments as to the significance of differences we see is just that they lack these two qualities.

In the development of all such general characteristics as these, environment too plays a large part. Its influence may even preponderate in many instances. For example, while the variability in height within the Japanese nation and within our own is probably by and large genetic, recent observations show that at least a very considerable part of the *average* difference in stature between Japanese and Americans is a result of the relatively deficient Japanese diet. This is substantiated by the fact that our own people have been gaining in stature, generation by generation, and children of immigrants, especially, tend to be taller than their parents. The whole question of the relative importance of heredity and environment is so vast and significant for our thinking that we shall return to it for fuller consideration at the end of this chapter. Meanwhile let us see what is understood about the way in which the genes control the production of traits, that is, how they regulate the characteristics of the internal environment.

THE PRODUCTS OF GENES INTERACT IN THE CYTOPLASM

The cytoplasm forms the environment of the genes. From it they must receive needed substances; to its conditions they are adapted; and whatever effects this community of reproducing proteins can bring about in the organism must be achieved by their modification of their immediate environment. In this respect the society of the genes strictly resembles our own.

Perhaps these considerations border on the obvious. Yet it is just here that our ignorance is most abysmal. Biochemistry has made enormous strides in the past century, yet we know little about the intricate series of reactions leading to the final production of even a single trait.

It is certain, however, that *many genes are limited in their effects to the cell in which they lie*. There are two ways of testing this. One is to study the effects of nondisjunction or

crossing over in body cells. Either of these rather infrequent events may render a cell homozygous for a recessive gene for which the rest of the body is heterozygous.¹² We might expect this cell and its descendants to be no different from the neighboring cells if its traits depend upon diffusible or circulating substances. If, on the other hand, the gene products¹³ are confined to the cell in which they are manufactured, the homozygous group of cells would differ from the surrounding heterozygous cells and form a distinctive spot. In the fruit fly a large number of genes have been tested in this way, and of them all only two or three appear to involve the production of diffusible substances. In plants, too, variegation in flowers, leaves, or seeds is very frequent. While hormones are, no doubt, much more important in vertebrate development than in that of insects, there is some evidence of mosaicism even among the vertebrates. Many of us have seen people with differently pigmented sectors of the iris or with eyes of different color. A few years ago the illustrated papers featured a child whose head showed a sharp division exactly down the middle, with brunette complexion, dark hair, and brown eye on one side, and blond complexion, sandy hair, and a blue eye on the other. This lad in a way resembles the insect gynandromorphs, which result most commonly from the loss of a sex chromosome in one of the first two cells formed during development. These oddities are male on one side and female on the other, and sex-linked recessive traits show up on the male side.

The other experimental method of testing the autonomy of genes within their own cells is through the technique of transplantation. Genetic research in America was still young when experimenters at Harvard University (W. E. Castle

¹² For an account of the way in which this is brought about, see A. H. Sturtevant and G. W. Beadle, *An Introduction to Genetics*, pp. 344-347 (W. B. Saunders, Philadelphia, 1939). This textbook is most highly recommended.

¹³ This can be taken to mean either substances directly produced by the gene, or those produced in the cytoplasm as an indirect result of the gene's abstraction of substances from it and its consequent alteration.

and J. C. Phillips) tried removing the ovaries of an albino guinea pig and implanting those from a black female in their stead. The operation succeeded, the female was mated to an albino male and had six young—all black! This showed that the dominant genes for black coat present in the implanted ovaries had not been altered. No doubt this was to be expected, since the genes in the implanted ovaries and, subsequently, in the "black" embryos were not exposed to any more radical influences than are usual for embryos. And embryos, although exposed to the maternal environment, in most cases develop according to their own genotypes, not their mother's.

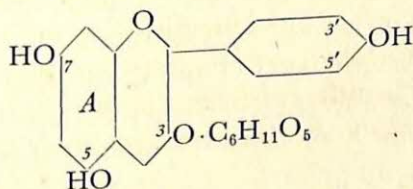
Rudiments of the adult eye may be transplanted from a fly larva into the abdominal cavity of another larva. They will then develop into complete eyes, pigment and all, except that they will be inside out. This technique provides a means of testing whether the genes for eye characters are autonomous, simply by introducing eye buds of one genotype into hosts of a different genotype. The results fully confirm those obtained by the other method. Of all the numerous eye characters tested, only two ever showed any influence of the host upon the implant.

Superficial transplantations from one species of salamander to another have also been tried. Here it was found that transplanted cells retain such characteristics of their origin as pigmentation and cell size, even though they may migrate considerably. On the other hand, they may enter into the formation of various parts of the host, according to their position. This is different from the rudiments of an insect's organs, which when transplanted have their fate already predetermined.

These instances of the limitation of a gene's action to a single cell suggest that the genic products are held in by the cell membrane. If the nuclear membrane is like the cell membrane in its permeability toward these substances, perhaps its dissolution at the time of mitosis is the means of

releasing the dammed-up genic products. This would explain why development and cell division ever accompany each other, and why, as the rate of cell division slows down, the course of specialization also draws to a close.

The extent of our knowledge and ignorance in this field will show up most clearly if we examine the best analyzed case, that of flower pigments. Some flower pigments (yellow and orange) are insoluble and located in plastids. Others, the anthoxanthins (yellow, ivory) and the anthocyanins (red, purple, and blue), are dissolved in the cell sap. Color variation may be due to the concentration of these pigments, but other changes are also important. The anthocyanins are hydrogen ion indicators, and vary from red at the acid end of the scale to blue at the alkaline. Some pigments, such as the ivory one, combine loosely with anthocyanins and produce a disproportionate bluing effect; these are the co-pigments. Finally, additional hydroxyl groups or sugar residues or a loss of methyl groups or organic acid residues, all make the anthocyanins bluer. Thirty-five genes from fourteen species or genera of plants have been studied, and *in every instance the biochemical action of each individual gene is a simple affair*. Thus the scarlet pigment pelargonidin may be rendered bluer by a dominant gene which adds an OH group at position 3'. Another dominant gene is then capable of adding another OH group at position 5',



making the flower color still bluer, while a third dominant gene is capable of adding on both groups at once. Still further cumulative blueness may be obtained by a dominant gene which adds a sugar residue at position 5 and by another which is responsible for the production of the ivory co-

pigment. There are also dominant genes acting in the reverse direction; in other words, there are both dominant and recessive genes for blueness. For instance, a single dominant gene may methylate the OH group at position 3' (changing it to $-O.CH_3$). Another methylates both the OH groups at 3' and 5'. A third adds an organic acid residue at some as yet unknown position. A fourth renders more acid the pH of the cell sap in the flower petals, and in them alone. All these factors make the pigment redder. Without multiplying examples, we can see that the dominant genes which bring about a specific change in the pigment molecule all *add* something to it. Their recessive alleles are inactive.

The anthocyanins and anthoxanthins are extremely similar in constitution and are apparently produced only at one another's expense. This implies that they must compete for some common precursor, which is probably the ring marked *A* in the formula. There is a gene in the snapdragon (*Antirrhinum*) which is essential for the production of both anthocyanin and anthoxanthin pigments and so must relate to the common precursor. The genetic changes in the other part of the molecule are probably accomplished before the final synthesis of the molecule.

This situation may appear at first glance extremely complex, yet it is far simpler than we might have expected. The simple biochemical action of any one of these genes leads us to hope that it is not altogether beyond the scope of our analysis. Perhaps there is here only a single chemical step, or very few, between gene and known biochemical effect. Analyses of the dosage effects of genes tend toward the same conclusion. Vitamin A in maize endosperm is produced from a yellow carotinoid pigment. A dominant gene (*Y*) is a factor for producing this pigment. Since endosperm is triploid, the effect of the *Y*-gene can be compared in dosages of 0, 1, 2, and 3 units. The vitamin A content of the grains is approximately proportional to these gene dosages. The gene can hardly be acting as an enzyme here, for enzyme concentration

is rarely related directly to the amount of the product. The immediate product of the gene may be some component or precursor of the yellow pigment. Recessive genes, too, are frequently found to approach the action of their dominant allele as their dosage is increased. They appear to be "doing the same thing—but less efficiently."¹⁴ The extreme of inactivity is represented by deficiencies. These are usually lethal; but when they are not, they may, like the deficiency for yellow body color in *Drosophila*, resemble the recessive alleles in effect.

Yet we must beware of oversimplifying the problem. We must remember that even genes concerned with but superficial traits, judging from mere inspection, have proved to be vital to the cytoplasmic system. Where each gene may be concerned with a number of traits, even determination of its particular time and mode of action upon a certain biochemical system very likely only opens up a lifetime of research to be pursued ere the gulf between gene and phenotype can be finally bridged by our chemical equations.

At present, about all we can say is that most genes probably affect developmental reactions through control over either their rates or their durations. A classical example is the process of pigmentation of the eye of the crustacean *Gammarus chevreuxi*. The black-eyed form is dominant; scarlet is recessive. During development the eye first appears scarlet. Then, in the presence of the dominant *B*-gene, it gradually darkens, becoming first brown, then chocolate, and finally black. When the genotype is homozygous for the recessive (*b*) allele, the process is the same, except that darkening starts later and proceeds much more slowly, consequently being brought to an end at an earlier point in the process. Very likely the pigmentation of our eyes and skin is determined in a similar manner.

Now chemical reactions in general are susceptible to con-

¹⁴ Sturtevant, A. H. and Beadle, G. W. *An Introduction to Genetics*, p. 337. W. B. Saunders, Philadelphia, 1939.

trol in rate (a) by physical factors such as temperature, light, or the degree of dispersion of the substances; (b) by chemical factors such as pH, or variations in the concentrations of the reagents; and (c) by catalysts. In the case of flower pigmentation, we have already seen how a gene which controls the pH in a localized region of a plant, the flower petals, may control the end-result of a developmental process. However, since physical factors generally either are beyond the control of the organism or are kept rigorously constant, it is, no doubt, through the other two avenues that most rate-genes operate. The Y-gene in maize may be taken as an example of those genes which control rates by varying the available amounts of precursors. Genes which control growth by controlling the production of glutathione (see Chapter I) exemplify control of a trait by means of enzymes. Inasmuch as the enzyme may not be an immediate product of the gene, obviously both types of control may be involved in any single chain of processes.

Control over the duration of a process upon analysis turns out to be a matter of rates, too. This is because the onset and cessation of a process likewise depend upon physical factors, reagent concentrations, and enzymes. Especially important in this connection are two phenomena, *threshold* and *maximum response*.

There is quite generally a minimum concentration which the substances determining a reaction must reach before they can act—this is the threshold. Together with the fact that, from individual to individual within the same genotypic class, there is normal variation due to "chance," the existence of thresholds is responsible for a considerable part of the confusion and difficulty in our thinking, past and present, about heredity. For when the effect of a particular genotype lies close to the threshold, normal variation will cause some individuals to fall above it and others below it. In other words, individuals of the same genotype may differ in phenotype. Human heredity abounds in such instances, especially among

hereditary diseases due to dominant genes. Such incomplete dominants, sometimes producing the disease and sometimes not, include hemolytic jaundice, a non-sex-linked type of hemophilia, polydactyly, and many others. It is, however, often difficult to determine, without recourse to experimental breeding, whether a trait is due to an incomplete dominant or to the interaction of two or more genes.

Above a certain point, either at the threshold or higher, any further increase in gene potency or dosage is without result. This is the principle of maximum response. It also has a relationship to the dominance of genes. For a gene to be completely dominant, it must produce the determining substance in such excess that no fluctuation of the environment will reduce it in amount below the threshold. Yet all alleles which exceed this limit will produce the same phenotype (in a common environment), since the concentration of the gene product is no longer a limiting factor in the processes of development.

Between threshold and level of maximum response there may lie a region in which increasing gene potency or dosage results in greater amounts of the gene product, and this is correlated with increasing manifestation of the trait. Figure 54 (p. 188) shows how these concepts may be applied to the white eye-color series of alleles in *Drosophila*, a typical series with the highest alleles dominant and the lower ones blending.

Both modifying genes and environmental factors can alter phenotype and dominance. This they may do by changing the time at which production of the determining substance is begun or ended, or when its effective production is ended; by changing the level of maximum response or the threshold; or by directly affecting the rate of production of the gene product relative to the rest of development.

Whether or not all genes act in this fashion, through control over rates of reaction in a quantitative way, is at present highly controversial. Perhaps completely different or "quali-

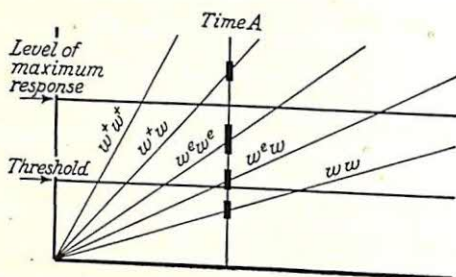


FIG. 54. A diagram to illustrate the relation of genic action in a series of alleles to thresholds and levels of maximum response. The effect produced by any genotype is indicated by the height at which the line representing its rate of production crosses the vertical line marked "Time A," at which the process under a given set of conditions is cut short. If the production line fails to reach the threshold by the time limit, no effect is produced. Any production line reaching the level of maximum response before reaching the effect is roughly proportional to height above the threshold. The normal variation of each genotype is shown by the thickened bars where the production lines cross the time line. Should the normal variation of a genotype overlap either the level of maximum response or the threshold (see $w^e w$), some individuals of that genotype would resemble the complete dominant or the extreme mutant, respectively. w^+ , normal allele of the white eye-color series (*D. melanogaster*); w^e , eosin; w , white.

tative" changes are also fairly frequent. But since we know nothing whatever of the mode of action of such changes, let us pass on to less speculative matters.

Here one might well raise the question whether we are really justified in assuming that all heredity is genic, and that the cytoplasm plays only the part of a substrate in which the effects of the genes are worked out. There is certainly still room for controversy. However, except for a few cases where certain plastid characters in plants are directly transmitted, there is no indisputable evidence of any specific hereditary character transmitted through the cytoplasm. Nor are the majority of plastid characteristics directly inherited; most of them, on the contrary, are clearly determined by genes.

Nearly all instances of "maternal inheritance," which might be supposed to depend on cytoplasmic heredity, since only

the mother transmits cytoplasm to the offspring, have now been found to be simply cases of delayed genotypic action. Thus the color of a silkworm moth's eggs is determined by her genotype rather than by that of the fertilized egg itself. In the mealmoth *Ephestia* the color pattern of the larva is determined by the maternal genotype through the first two molts. Then the larval genotype, with its paternal contribution, becomes effective, and thus may produce a striking change.

Often in crosses between different species or genera there is an effect of the maternally derived cytoplasm upon certain gene-determined traits; that is, reciprocal hybrids may consistently differ somewhat in phenotype, even though identical, as far as we can tell, in genotype. Their offspring, in turn, show the same tendency to resemble their mothers in these respects. These observations simply mean that genes tend to act differently in different cytoplasmic substrates. There is also evidence that they work better in that of their own species than in another, while in very foreign substrates they cannot operate successfully at all. This does not mean that the cytoplasm has hereditary qualities like those of the genes. It is simply another indication of the interdependence of the genes and their immediate environment, which have become attuned to one another through eons of evolutionary adaptation.

On the outside, the cytoplasm is exposed to the conditions of the external environment and so is subjected to modification. Some of these changes are transitory; others may be quite enduring. The effects of exposure to extreme temperatures or to chronic alcoholic poisoning upon the cytoplasm of germ cells—or of vegetative tissues that give rise to offspring asexually—may be handed down for generations before they finally disappear. Even the general adaptation to particular conditions of life—climate or diet, for example—may be of this sort, a pseudoheredity that would be readily mistaken for the work of the genes themselves, were it not

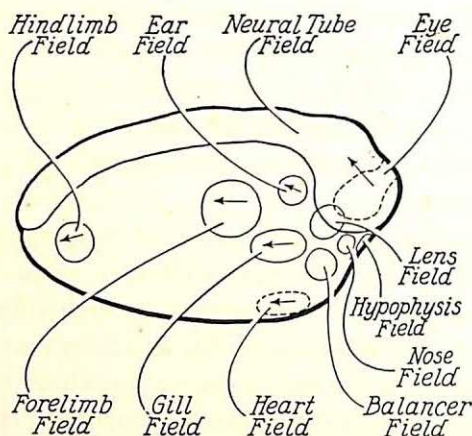


FIG. 55. Diagram of an amphibian embryo to show the approximate localization of the main districts (unfortunately labeled "fields") known from experiment. The arrows indicate that the districts are polarized from their first appearance. The arrows indicate that the districts are polarized from their first appearance. *Hypophysis* is a synonym for pituitary gland. The balancers are organs growing on the outside of the tadpole's throat region. (Redrawn from Huxley and DeBeer's *The Elements of Experimental Embryology*. Courtesy of Cambridge University Press. By permission of The Macmillan Company)

correlates the growth of different parts. Thus, if an arm bud (a district) is grafted onto the spot from which a leg bud is removed, it will develop into an arm, but its size will be that of a leg. It appears, therefore, that the primary axial gradients and their fields are responsible for the pattern of the organism as a whole, while the organizer-districts lay out the minor regions for the several organs.

Another example of an organizer may be taken from a later stage in development. After the front end of the neural tube has developed into three bulges which will later make the brain, two side pouches grow from the front one, the forebrain. These extend until they reach the ectoderm, growing into the form of cups on slender stalks. If, now or earlier, this part of the forebrain is cut out and transplanted beneath the surface layer, either of the same embryo or of another of an age not too much older, it will induce the ectoderm to fold in and assist in producing an eye in the normal fashion

(see Chapter V, pp. 289 f.). Just anywhere—for all the ectoderm is potential eye material! In this way you may produce as many eyes as you wish, although, unless they are connected to the brain, they will naturally not be able to contribute to vision. The side pouches of the forebrain are the eye organizers.

Hormones which have specific effects during development are now being discovered in abundance. Some act early in development, some late. There is a South American blood-sucking bug (*Rhodnius*) which can molt only at an interval after having had a big meal of blood. If it fails to get a real gorge, it consequently cannot grow or mature. The molting normally results from the production of a hormone by a gland near the brain. The hormone circulates through the blood and sets the epidermal cells, long quiescent, into rapid cell division. This hormone is effective not only in closely related species but even in as distant a relative as the common bedbug, which belongs to a different family. It is, in fact, a general rule that hormones have similar effects on a wide variety of related organisms.

Perhaps no better example than the one just described can be found for revealing the involvement of genes, cytoplasm, organismal and environmental factors in development. Here we behold an environmental variable (a good meal) acting as the trigger which sets going a localized physiological process that is itself an expression of hereditary potentiality. This physiological process is the secretion of a hormone to which only certain tissues of the body, the epidermal cells, are responsive. The responsiveness is, no doubt, a matter of cytoplasmic attunement. Finally, mitoses are set in motion; the genes in these cells are themselves stimulated to activity; growth takes place; a new cuticle is laid down, and the old is molted. The type of cuticle, whether immature or mature, is seemingly determined by another hormone emanating from the same gland as the molting hormone.

In *Drosophila*, too, a molting hormone has been found.

strictly maternal or somatic in transmission and far less enduring.

The genes are thus buffered from the outer environment by their own surrounding cytoplasm. In many-celled organisms, each cell in its turn lives in the midst of a multitude of its fellows, constituting a larger living environment interposed between cell and outer world. This must also be considered.

THE ORGANISM DURING DEVELOPMENT REACTS AS
AN INTEGRATED WHOLE

At no time in our development after the first cell division or two, are we simply an agglomeration of cells. Always we are something more than the mere sum of heart plus brain plus digestive tract plus other organs. For at the outset the whole organism, as yet relatively simple in organization, performs all essential functions in a general way—as a whole. As development proceeds, parts of these general functions are delegated to each specialized structure. Yet no matter how autonomous they become, they can operate only if other parts of the body carry on the remainder of the general functions for them. Hence, *the more specialized are the parts, the more integrated is the whole.*

If this seems abstruse, perhaps it may be more readily understood from an analogy with the molecule. A molecule of cane sugar (sucrose) is more than the mere sum of twelve carbon atoms, twenty-two hydrogen atoms, and eleven oxygen atoms. These must also be arranged in a particular pattern, for the same atoms, in various other relationships to one another, may form maltose, lactose, or any other disaccharide. Our present problem, then, is that of bodily pattern. How is the abstract pattern of the genes, a haphazardly arranged collection of potentialities, related to the visible, functionally arranged and integrated pattern of the body produced by development?

The primary foundation of form lies in *the fixation of the axes which determine the symmetry of the body*. The first of these is already predetermined in the egg through the differentiation of animal and vegetal poles. In many species, as yolk is stored in the egg during its growth in the ovary, it tends to gravitate to the vegetal pole, while cytoplasm and nucleus occupy the animal pole. Many biologists have tried to find the reason for this first visible indication of the egg's polarity. Most of them have come to the conclusion that some factor external to the egg is responsible. Perhaps the position of the egg in the ovary allows one end readier access to oxygen than the other. At any rate, a gradient of metabolic activity is set up in the egg, and this would appear to be true even of such eggs as have evenly distributed yolk, like those of mammals. This metabolic gradient seems to fix the initial axis of the egg, and our anterior (head) and posterior (hind) ends come, respectively, from the animal and vegetal hemispheres.

Every cell produces electricity as one of its characteristic forms of energy. Since cells formed at the animal pole are more energetic than the inert, yolk-filled ones at the vegetal pole, that end of the embryo is *positively* charged with electricity. In at least some organisms, it is clear that this electrical polarity has been established as the controlling axis of development by the time all the yolk is used up.

Our primary axis is thus fixed even before fertilization, but any of the infinity of meridians from pole to pole can apparently become the dorsal-ventral (back-to-belly) plane. Just how this is determined seemingly depends upon the influence of some aspect of the environment—perhaps, as in frogs, it is a matter of where the sperm enters the egg, this meridian becoming the mid-ventral line, and the opposite one the dorsal. However that may be, *the fixation of this plane lays the foundation for bilaterally symmetrical development*. Right and left of this plane the sides begin to develop as mirror images of each other.

In general, the gradients of activity run from head to tail, from back to belly. The cells toward the head divide faster and, consequently, are smaller than those to their rear. Similarly, cells along the back divide more rapidly and are smaller than those ventral to them. Since the gradients are not merely axes, but involve cell layers and masses in the developing embryo, it is better to speak of the whole mass of cells influenced by any particular gradient as a *gradient field*.

Next comes the localization of substances. Some are already localized in the egg, as is the yolk. As cell division proceeds, others are also localized, under the influence of physical factors such as gravity, and no doubt more especially because of the polarity of the embryo. These substances must include also the products of such genes as commence activity at this time or earlier. Such secondary enzymes or precursors, once localized, play an important part in the further development of form. They have been called *organizers*, the hormones of development.

The best known of these affords a striking example. When the embryo has grown to resemble a sack with only a small opening to the exterior (for a detailed account of the process see Chapter V), the nervous system begins to form as a groove which extends from the dorsal lip of the pore toward the head end. This groove deepens, the walls fold over to make a tube, and the nervous system thus originates from the surface layer of the body. Now we might ask—could any portion whatever of the surface layer, called the *ectoderm*, do this—and make a complex brain and spinal cord? This question has been answered by ingenious experiments upon frog and salamander embryos. If the dorsal lip of the pore is cut away, and the tiny piece transplanted to another position, a groove will extend from it toward the head end, and shortly we can see a neural tube in process of growth. Or transplant these particular bits of tissue from several embryos into one, and you may produce as many neural tubes as you wish! *Any part of the surface layer possesses the capac-*

ity to develop into a neural tube, but does so only when stimulated by a particular organizer, which is the substance (or substances) localized in the dorsal lip of the pore.

We can be sure that chemical substances, and not some influence of the living tissues, are responsible for this effect, for dead material or extracts from the same source are just as effective as the living organizer.¹⁵ However, there is a difference in the way a transplanted dorsal lip organizer acts upon head and trunk. It appears, in short, that the organizer substance merely induces the surface layer of the body to form a neural tube, while the regional characteristics of the neural tube depend on the "axial gradient," or polarity, already established.

If we delay transplanting the organizer until the surface layer of the host embryo has already reached a certain point in its normal differentiation, the organizer will have no power to reverse the changes that have occurred. In other words, the organizer acts only on cells below a certain stage of specialization—beyond that the chemical and physical setting of the protoplasm is no longer one in which this hormone can affect matters. *Districts can be delimited which have become fated to form particular organs* (Fig. 55, p. 194), each district having a polarity of its own.

These districts are somewhat different from the gradient fields about the axes of polarity. The latter are based upon dynamic equilibriums, and the dominant regions of such fields can activate or inhibit at a distance. A fragment of such a field tends to reorganize itself so as to make a miniature whole. On the other hand, the districts, which depend upon a gradient in the concentration of some substance, are, once outlined, of predestined fate. They do not depend upon equilibriums, but upon a superthreshold concentration of a particular organizer. Their own polarity may be swamped by that of the broader primary gradient, which apparently

¹⁵ The analysis of these extracts indicates that at least some of the organizers belong to the group of sterols.

But more interesting in this organism are the diffusible substances involved in the production of normal eye color, for these—two are known—are each dependent upon a particular gene (vermilion and cinnabar). One of the hormones (the v^+ hormone) appears to be a precursor of the other (the cn^+ hormone); for, while eye buds from larvae of either vermilion or cinnabar genotypes become red (normal) when implanted in wild-type hosts, the results of reciprocal transplants of vermilion and cinnabar are different. A “cinnabar” host can supply a “vermilion” implant with the substance it lacks, and produce red eye color; a “vermilion” host cannot do this for a “cinnabar” implant. These two hormones have been extracted from various tissues, and, although not yet completely analyzed, it is clear that they are not proteins but are of a simpler chemical constitution. Probably they are amino bases produced by protein breakdown. They do not behave as enzymes. These facts make it seem likely that the normal eye color is, so to speak, a by-product utilizing the waste of some more vital process.

Scarlet is another recessive gene affecting the eye color in a manner indistinguishable from vermilion or cinnabar phenotypes. Yet “scarlet” larvae have both the v^+ and the cn^+ hormones in abundance. One or the other of them must somehow be kept from use. Here is a single phenotype which can be brought about by any one of three (or more) genes, each having its own individual mode of action. This situation should help us to understand the many instances in human heredity where a certain trait, such as hemophilia, is commonly sex-linked, but not always; or where, as in the case of congenital night blindness, a trait is a simple dominant in some families and in others a sex-linked recessive.

In the mealmoth (*Ephestia*) and in a wasp (*Habrobracon*) parasitic upon it, there are also recessive eye colors (red and ivory, respectively). The normal alleles of these genes are also responsible for the production of eye-color hormones. It is a startling indication of how similar a biochemistry may

underlie the development of distantly related forms to discover that the known hormone in the mealmoth is the same as the v^+ hormone of *Drosophila*, while that of the parasitic wasp is identical with the cn^+ hormone. Perhaps the very genes themselves are identical, although there is at present no way of knowing.

In plants, too, hormones have been discovered which play an important role in growth. These are the three *auxins* (see Chapter I, p. 38), some one of which is apparently present in every plant. They bring about the elongation of cells even in unbelievably small concentrations; when applied to only one side of a growing oat sprout, 1 mg. of either auxin *a* or auxin *b* would be sufficient to cause a 10° bend in each of 50,000,000 shoots! Heteroauxin, the third of the trio, and already successfully synthesized,¹⁶ is only half as potent. Auxins are formed in the growing tips of stems, buds, leaves, and branches, and diffuse toward the base of the plant and on down into the roots. Here, too, there are cells of the particular age and character that are sensitive to the auxin, and even more so than those aboveground. The concentration which evokes maximal growth in the root cells is only about 1/10 of that required for buds and only 1/100,000 of that required for stems. The result is that growth by elongation takes place in a root only while it is very young and tiny, and is soon done, before the root hairs begin to form; whereas stems may continue to lengthen over a much longer period.

The response of a growing plant to light or gravity is also based upon the presence of an auxin. As for gravity, it appears that auxin tends to accumulate on the lower side of a horizontal stem; this side then grows faster than the upper, and the stem curves upward until the concentration of auxin becomes equal around the stem. Similarly, auxin accumulates to a greater extent on the darker side of a stem, so that it curves toward the light. On the other hand, be-

¹⁶ All three auxins are monobasic organic acids. Heteroauxin is indole-3-acetic acid.

cause of the greater sensitivity of the root to auxin, its elongation is inhibited by the same concentration that stimulates the stem. A horizontal root, therefore, grows down because the accumulation of auxin on the lower side inhibits elongation there more than on the upper side. In this way *the same environmental factor acting on the same internal agent may yet produce strikingly different results in various parts of an organism because of the earlier differentiation of those parts.*

To see how the genes may regulate this biochemical mechanism of growth control, we need only look at the dwarf mutant form of maize known as *nana*. In this recessive type auxin is destroyed faster than normally, and curtailed growth is the consequence. In man the recessive gene which produces midgets probably acts through the endocrine glands in a somewhat similar fashion.

All of the preceding instances of hormones at work in growth and development may help us to understand the still more complex nature of our own development, and the role of hormones in it. Because we have already devoted much attention to the genetic aspects of sex, the hormonal control of sex differentiation should make a good example.

We may recall that in all individuals there exists a potentiality for producing the sexual characters of both sexes. All male organs have female counterparts, and vice versa. Moreover, with the exception of the ducts which provide outlets for the reproductive cells, these corresponding organs always develop from the same buds. It is the direction in which the development proceeds, or the degree to which it extends, that determines final differences. The story is therefore one of complementary inhibitions and stimulations.

Let us start with the gonads. As they first develop, each consists of an inner core (or medulla) of male tissue and an outer ring (or cortex) of female tissue. Each of these forms a hormone, which works antagonistically upon the tissues of the opposite sex, at the same time inducing more vigorous

growth in the tissues of the same sex. In some way the genotype (XX or XY) determines which element will get the upper hand, and before long the other is first inhibited and then commences to dwindle (see Fig. 56). In the male the female tissue eventually disappears completely; in the female a small remnant of the male issue is left, so that a female under certain conditions may develop intersexually.

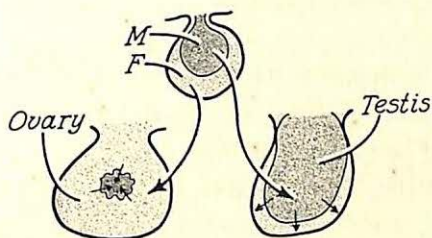


FIG. 56. Diagram to illustrate the alternative development of ovary and testis from the same type of rudiment (upper center), consisting of both male tissue (M) and female tissue (F). The small arrows indicate the predominating secretion in each case. The larger arrows indicate the tissue in the rudiment that becomes predominating in ovary and testis, respectively. (Redrawn from Burns, after Witschi)

This general interaction reminds us of the man who lifted himself by his bootstraps—for the more hormone one element of the gonad secretes, the more it inhibits the other element, and the more it stimulates its own further growth, so that it can secrete still more hormone. We should like to know what puts a stop to this! And what is the relation of these two hormones to the organizers which presumably cause the gonad to appear in the first place? Are they the same?

Observations upon conjoined twins of different sexes, or experiments, such as grafting a gonad of one kind into a host of the opposite sex, or castration, or the administration of various dosages of hormones, show us the further consequences of the interaction of these hormones. In birds and lower vertebrates sex may be completely reversed. In mammals this has not been found possible, but partial reversal is well known. A freemartin is a genotypically female calf that,

through conjunction of blood vessels with a male calf, has been subjected to dosage with the male hormone while in the uterus, until it has undergone partial sex reversal. The ovaries are destroyed early, and from then on the female hormone is lacking. This naturally has further consequences. The male calf is unaffected because testes develop faster than ovaries, and the male hormone therefore swamps the female.

By administering hormones, we know that large doses of either male or female sex hormones can induce both the male and the female ducts to develop. In smaller doses, however, each sex hormone appears to stimulate only the ducts of the corresponding sex. That is, the rudiments of the male ducts are more sensitive—they have a lower threshold for response—to the male sex hormone than to the female; and conversely for the rudiments of the female ducts.

While the sexual ducts appear to be responsive to both hormones, the external genitalia and the secondary sexual characters are, according to our present knowledge, affected solely by the male hormone. If you administer female hormone to a castrated animal nothing happens. But male hormone makes the castrate externally into a male, and will even modify the external sex structures of a female into their male counterparts. Of course, here the previous development as female will count for something and reversal will rarely be complete. The lack of any effect upon the external genitalia and upon the secondary sex characters by the female hormone at last explains why a male fetus develops these structures normally in spite of the abundant female hormone supplied by the mother.

A strange thing is that the germ cells themselves are not involved in all this. In birds, they originate elsewhere and make a long migration before getting to the site of the gonads. In mammals they may originate in the gonads, but only after these have accomplished a considerable part of their development. The gonads, and hence the other sex

structures, will develop quite normally in the absence of sex cells, but the animal will, of course, be sterile.

Our picture of sexual development in terms of hormones is still much too simple,¹⁷ but its general character is perhaps clear enough. To sum up, at definite locations in the body organizers lay out the districts for the gonads and their ducts. Since each gonad includes both male and female tissues, probably two organizers collaborate in inducing it to start development. Where these substances are first produced is uncertain, but they probably come to be concentrated at the appropriate points through the influence of the primary gradient fields. As the gonads increase in size, the male and female portions commence to elaborate their respective hormones, which are perhaps chemically the same as the gonad organizers. A conflict of self-stimulation and reciprocal inhibition results; and one type of tissue, that favored by the genotype, overwhelms the other. Its hormone stimulates the corresponding type of sexual duct to enlarge. Finally, if it is the male hormone, it stimulates the external genitalia and secondary sexual characters to develop differentially.¹⁸

The attainment of ultimate size and form by the organs brings us to the third major group of developmental factors. The axes and planes of symmetry, and their gradient fields, lay out a ground plan of development. Organizers block in the details. *But the ultimate form depends upon*

¹⁷ We have, for example, said nothing here about the masculinizing effect of the hormone from the cortex of the adrenal glands upon the external genitalia and secondary sex characters, or about the general control of the pituitary gland over the activity of the gonads.

¹⁸ For further study of these problems, the reader is referred to such authoritative works as:

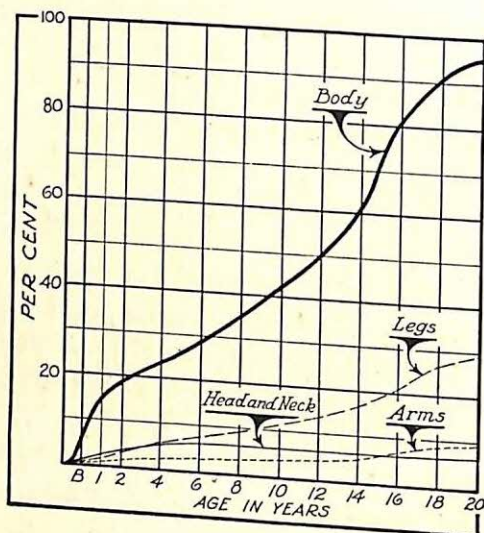
Huxley, Julian and DeBeer, G. R. *The Elements of Experimental Embryology*. Cambridge University Press, 1934.

Spemann, Hans. *Embryonic Development and Induction*. Yale University Press, 1938.

Allen, E., Ed. *Sex and Internal Secretions*, ed. 2. Williams and Wilkins, Baltimore, 1939.

See also Mohr, O. L. *Heredity and Disease*, pp. 164-188. W. W. Norton, New York, 1934.

relative growth rates. This means simply that some parts grow slower or faster than others. To begin with, for example, about three fourths of the body is laid out as head! Yet, since the head grows at a consistently slower rate than the rest of the body, two months later the head is not quite as large as all the rest, at birth it is about one fourth as large,



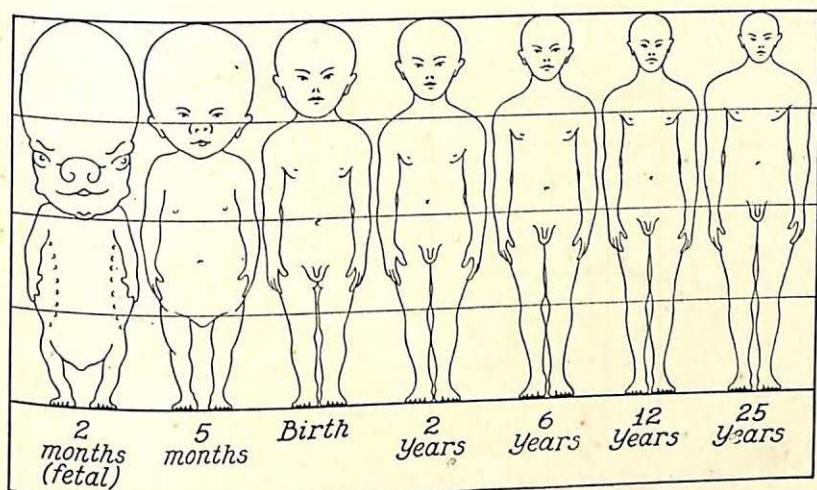
A

FIG. 57. A, growth curves of head and neck, arms, and legs compared with that of the whole body to show differences in relative growth rates.

and at maturity it is only 7 per cent of the total bulk of the body.

Our limbs do not even appear until the fifth week of our prenatal development. The limb bones alternately lengthen and thicken (six months of each), and, moreover, some are lengthening while others are thickening. At two months our limbs are 6 per cent of the body's bulk, and arms and legs are equal. At birth, seven months later, they make up nearly one fourth of our body, but our legs are almost twice the size of our arms. (Have you ever noticed the gangly proportions of newborn lambs or colts? The higher relative growth rate

of limbs before birth is evident there too, although thereafter the growth of their legs slows down.) At maturity our limbs are 40 to 50 per cent of the body's bulk, but our legs are three times the bulk of our arms. No wonder, then, that babies are so different from adults, with their heads so much larger in proportion to their legs. We may represent these



B

FIG. 57 (Cont'd). B, changes in form and proportion of the human body during fetal and postnatal life. (B redrawn from Morris' *Human Anatomy*, ed. 9. Scammon, after Stratz. Courtesy of The Blakiston Company)

growth rates graphically by curves showing the increase in bulk with age (Fig. 57).

Organs may grow at the same rate as the whole body. As long as this is true, increase in absolute size is not accompanied by any change in relative size. But, as we have just seen, other organs grow at a rate different from that of the body as a whole, or an organ may grow at different rates in different dimensions—this is the phenomenon of *heterogony*. Since it is extremely unlikely that any animal will not have some heterogony, it follows that *all animals must alter in form as they alter in size.*

One of the most striking facts learned about growth is that, where heterogony obtains, *the ratio between the two different growth rates remains constant for long periods during development.* In spite of the fact that both growth rates are

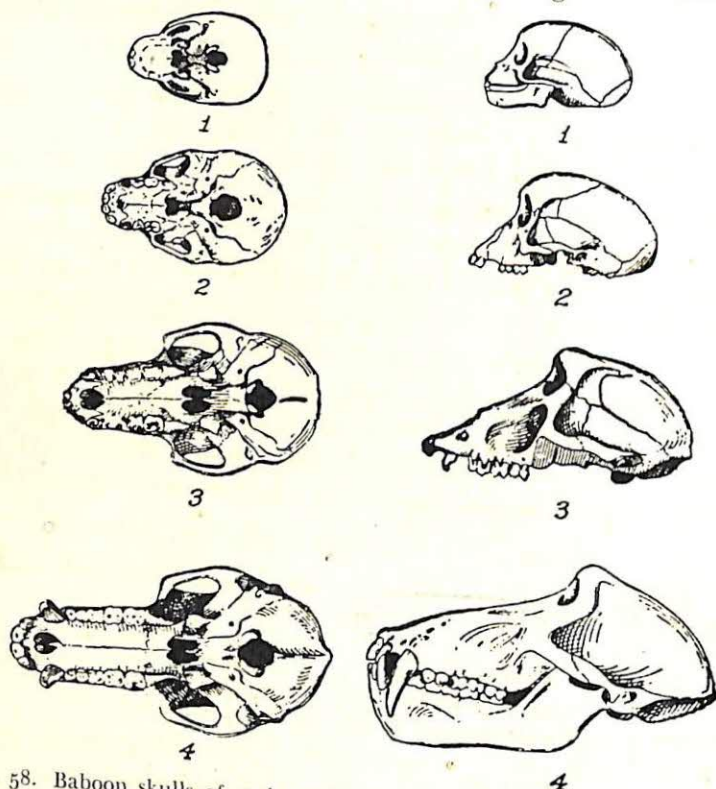


FIG. 58. Baboon skulls of various sizes, to show the increase in relative size of the facial region with absolute size of skull. (1) newborn; (2) juvenile (with milk dentition); (3) adult female; (4) adult male. (From Huxley's *Problems in Relative Growth*. Courtesy of The Dial Press)

usually changing, for growth tends to slow down with age, they remain related to each other in a constant way.¹⁹ This

¹⁹ This can be expressed mathematically in the form $y = bx^k$, where x and y are the magnitudes of the two differentially growing elements, b is a constant indicating the value of y when $x = 1$, and k is the ratio of the relative growth rates. Since k is logarithmic, this means that growth is a character. In other words, the more growing material there is, the greater the access of fresh material.

produces a *progressive* change in relative size or form. The final form consequently will depend entirely upon whatever absolute size is reached. Examples of what is meant are so clear from pictures that it is scarcely necessary to discuss them. The facial part of a baboon's cranium grows at a faster rate than the rest of it, and the ratio between the two growth rates is constant. Figure 58 shows the result.

For many years researchers have wondered about the genetic basis of the differences between the queen bee and workers or between queen ant and the several varieties of soldier and worker ants. Then it was discovered that the workers were all neuter females, sterile because fed by their nurses on a somewhat deficient diet. Now it seems likely that the big-headed, fierce-jawed soldiers and the small-headed, weaker workers also differ only environmentally. For there is positive heterogony of head over body; and the larger the absolute size a worker attains, the bigger its head and jaws become in proportion (Fig. 59, p. 206). It is the limitation in the total amount of growth that is the decisive factor. Here it is determined by nutrition; yet in another organism it might equally well be genetically controlled.

The constancy of the ratio of the growth rate of a part, such as a limb, to that of the whole body does not mean that all parts of the limb are growing at the same rate. After birth the hind legs or lower limbs grow more slowly than the body. Measurements show that the most distal joints are growing relatively slowest, and that there is a regular gradient of increasing growth from there to the trunk. Conversely, before birth, when the legs are growing faster than the body, the distal parts are growing fastest. So, whether the heterogony is positive or negative (that is, whether the differential growth rate of the part is faster or slower than that of the whole), this distal region is the *growth center* of the limb.

Since the growth gradients extending in the three planes of space from the growth center may differ, the composite of all growth centers and growth gradients in the body makes

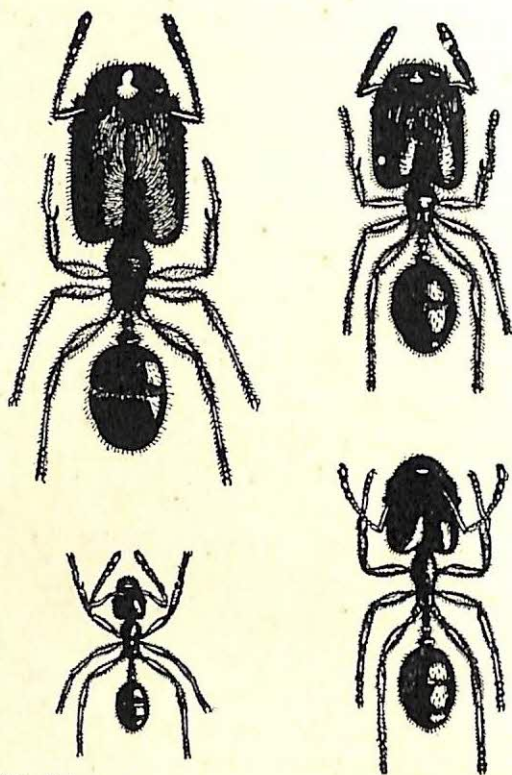


FIG. 59. Increase of the relative size of the head with absolute size of body in neuters of the ant *Pheidole instabilis*. Enlarged. (From Huxley's *Problems in Relative Growth*. Courtesy of The Dial Press)

up a complex growth pattern. More than twenty years ago D'Arcy Thompson pointed out that the differences in form between related species, even when extreme, might be interpreted as simple changes in the location of growth centers or in the relative magnitude of growth gradients. Thus the astounding shape of the great ocean sunfish may be derived from that of an ordinary-looking relative merely by distorting in a perfectly regular way Cartesian coordinates drawn about the figure of the latter (see Fig. 60). The sunfish has evidently acquired, over and above the growth pattern of its relatives, a sharp growth gradient running from a growth center at the tail toward the head.

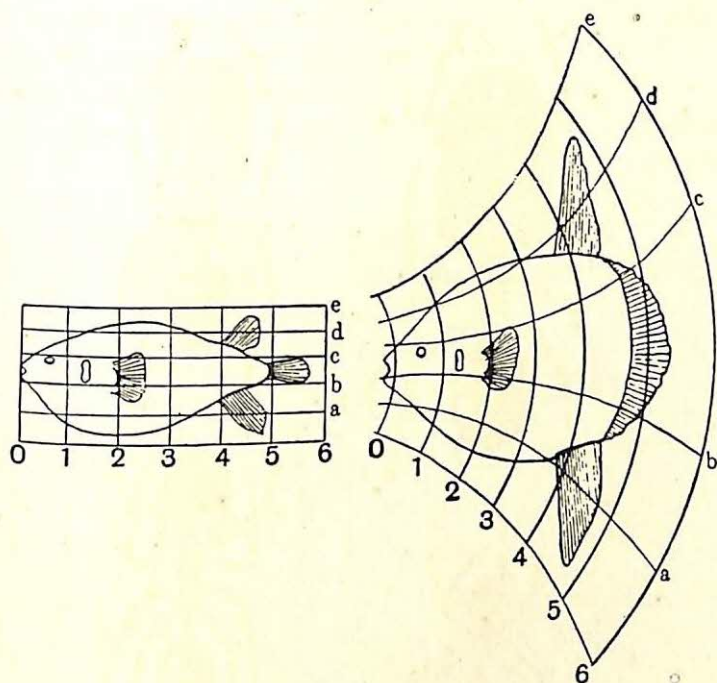


FIG. 60. Cartesian transformation of the outline of the fish *Diodon* to give the outline of the related sunfish *Orthogoriscus*. (From Huxley's *Problems in Relative Growth*. Courtesy of The Dial Press)

This is also illustrated in the formation of at least some human embryo monsters. In the first one shown on page 208 (Fig. 61A), there is marked underdevelopment of the head, accompanied by greater growth of the next posterior region of the body gradient. Hence the chest is enlarged, and a growth gradient runs from there out the arms, with progressively less increase over normal in upper arms, forearms, hands, and digits. In the second case (Fig. 61B) there is a relative increase in the potency of the growth center in the head, and a steeper gradient along the body axis.

Numerous are the instances of gene-controlled relative growth rates. The short limbs of dachshunds and basset-hounds are due to a single recessive gene in each case. The

"short-ear" gene in mice produces localized changes in the growth of the skull. In squashes and gourds there are genes for both size and shape, the latter controlling relative growth rates, so that the shape of each fruit changes progressively during its increase in size.

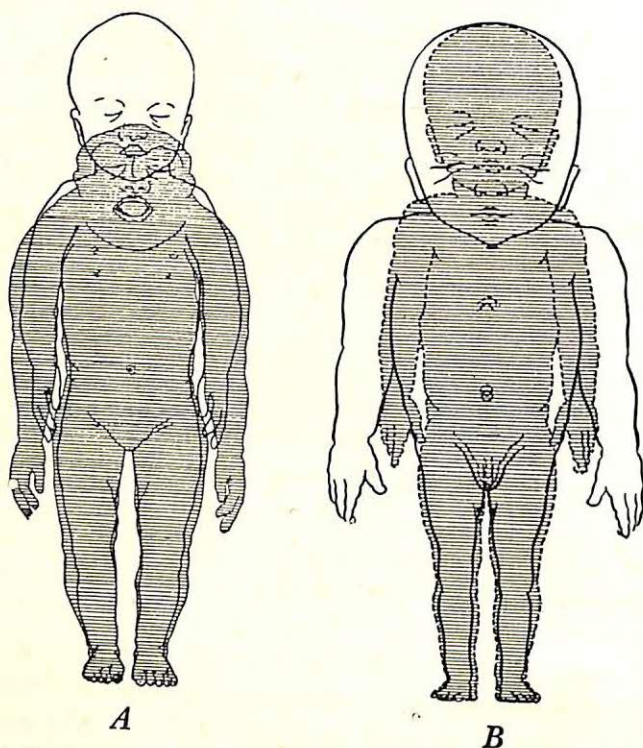


FIG. 61. Graded growth effects in two human monsters. In A, the normal infant is shown in outline, the monster is shaded; in B, the normal infant is shaded, the monster is shown in outline. For further explanation see page 207. (From Huxley's *Problems in Relative Growth*. Courtesy of The Dial Press)

If, on the one hand, the relation of relative growth rates to genic control is apparent, it is no less clear that they must also be related to the primary axes, to the delimited fields and districts, and to the hormones. In regenerating hydroid polyps the first region to differentiate acts as a dominant region controlling the development of the rest of the body.

Moreover, the location of this dominant region can be altered by external factors which either temporarily overwhelm the primary axial gradient, as an opposed electrical gradient can do, or completely wipe it out, as do weak poisons. Here the production of form during growth, a matter of local differences in growth rates, is clearly subject to the larger, fundamental growth pattern of the whole.

If you transplant an organ from a slow-growing salamander to a fast-growing one, it will continue to grow slowly. Conversely, if you transplant an organ from a fast-growing salamander to a slow-growing one, it will maintain its own inherent growth rate. This shows that the localized growth centers and gradients are related to the districts of the embryo induced by the localized concentration of organizer substances.

Finally (1) the distinctive growth of the sex organs in male and female under the influence of the sex hormones, (2) the preponderant stimulation of limb growth in pituitary gigantism, and (3) the action of thyroxin in stimulating the growth of internal organs (heart, lungs, liver, kidneys, spleen, adrenals, pancreas) while suppressing that of the pituitary gland—these show the relation of hormones to relative growth rates.

A further aspect of heterogony which particularly concerns us is the appearance of asymmetry on the two sides of our body. In all the higher, bilaterally symmetrical animals the later phases of growth show some degree of secondary asymmetry. Our stomach projects toward the left, and heart and intestines are spirally coiled. Dentition and facial features are somewhat asymmetric, and the crown-whorl of our hair spirals in a particular direction. One side of the brain also achieves a functional predominance over the other. All these seem to be due to the existence of growth gradients running from left to right, the most active growth usually being on the left. These in turn may be due to gradients in the distribution of auxin-like substances, for, if you cut out a piece of the roof of a tadpole's gut before its coiling com-

mences and replace it after reversing it 180 degrees, the intestine and heart will coil in the opposite direction to their usual one, and the stomach will also be reversed in position. Studies on the coiling of snails and other mollusks show that their asymmetry is already determined in the egg *before* fertilization. Moreover, it is determined by a single pair of alleles present in the mother.²⁰ In our own case, too, the development of left-handedness or right-handedness is predominantly determined by a single pair of genes. The greater frequency of right-handed people indicates that, because of the crossing of the nerve pathways in the brain-stem, most of us are left-brained. In other words, the dominant allele renders the left end of the growth gradient for the brain predominant; the recessive allele favors the right end. If it is permissible to put together this evidence assembled from different organisms, we have here a clear chain starting from the genes, and leading through concentration gradients of growth substances to the appearance of left-right growth gradients which finally result in phenotypic asymmetry.²¹

One more feature of development deserves a word. The early phases of the development of any structure as a rule take place before it begins to be of any use. Eventually it passes from this prefunctional stage to one of use, and this use definitely affects the further course of its development. We are all familiar with the stimulating effect of exercise upon the growth of our muscles, but it goes much further than this. The pull of the muscles orients the fibers of the attached tendons along the lines of stress. The finer architecture of the bones—the direction of the spicules and tiny

²⁰ This implies that the paternal contribution to the genotype as regards this pair of genes is delayed a full generation in its effect, for a dominant gene from the father will not determine the direction of coiling in the immediate zygote but in the eggs produced by that zygote after it has developed to maturity.

²¹ Classic reference on the subject of heterogony is *Problems in Relative Growth* by Julian Huxley (Lincoln MacVeagh, the Dial Press, New York, 1932).

struts which provide the spongy structure at their ends, and the denser, firmer structure in their shafts—this, too, depends on the direction of the stresses they meet. Anyone who has ever seen the wasted, bent legs of an invalid, or who has seen an x-ray picture of their curved, weakly bones, will know how great this effect can be. Use of the muscles and organs also determines the amount of their blood supply, and this plays a great part in fixing the number, size, course, and branching of the minor blood vessels. The severity and type of bacterial invasion regulate the total number and the relative frequency of the several sorts of white blood cells. Lack of sufficient iodine in the diet will cause the thyroid gland to hypertrophy, resulting in a goiter; and removal of one kidney will result in the enlargement of the other, which has to do double service. Even the character of the cells may be changed by use, as in one instance where the artificially induced hypernormal use of the urinary bladder in a dog caused the walls of this organ to become ten times thicker, the cells took on a striated character like that of heart muscle, and the whole organ pulsated rhythmically.

CAN WE ASSESS THE RELATIVE IMPORTANCE OF HEREDITY AND ENVIRONMENT?

At the beginning of this chapter we examined the problem of fat color in rabbits, and concluded that the potency of either heredity or environment can be discerned only when we isolate the effects of either one of them by rendering the other constant. We may see how easy it is to overlook the implications of this principle from the fact that, until recently, books on human heredity classified pellagra as a hereditary disease because it "runs in families," ignoring the fact that faulty nutrition (in this instance lack of nicotinic acid) is also shared, like many other aspects of environment, by those living under the same roof. Yet, with this clearly in mind, we must still face the practical aspects of our question.

Should we put our trust in eugenic measures, or should we work for a better future by improving our environment?

Now this is not to be confused with the old, erroneous distinction between hereditary and environmental traits. Rather, we are here concerned with four categories of relationship:

Genetic

1	Genetic differences manifested in practically all types of environment	Differences due to environment manifested only in a restricted range of genotypes	3
2	Genetic differences manifested only in a restricted range of environment	Differences due to environment manifested in practically all genotypes	4

Environmental

Categories (1) and (4) are the indisputable cases, such as the differences between color-blind or albino and normal, in the first; and between one who has accidentally lost an arm or an eye and one who has not, in the fourth. These two categories, however, include relatively few examples of differences. For instance, there is little besides mutilations in category (4). Categories (2) and (3), on the other hand, are extensive and include most of the traits we would like to control, and may possibly be able to.

There is, of course, a gradual transition from category to category. It is especially important to realize that different categories frequently include the same phenotype; that is to say, exposure to a particular environmental factor at a particular time during development will very likely produce an effect like that of some known gene mutation. Thus the phenotype of genetic rumplessness in chickens has been duplicated by treating eggs with abnormal temperatures during the first

week of their incubation. So, too, cretinism may appear in many genotypes, wherever the local supply of iodine is low; or, where the supply is adequate for the majority, it will appear only sporadically, in the few most susceptible genotypes. In the first kind of locality we might regard cretinism as environmentally caused, while in other regions it would appear to be hereditary. The fundamental fact, however, remains the same. Various genotypes have a differential susceptibility to lack of iodine; and this, along with the local abundance of the element, determines the incidence of cretinism.

An example that we can treat graphically may further help us to understand this point. In *Drosophila*, the number of facets in the eye is reduced below normal by the gene Bar and still more by its allele Double-Bar. The number of facets is also decreased by any increase in temperature during the susceptible period of eye development. However, the two Bar alleles do not act proportionally at different temperatures. The change in the effect of Bar with a shift in temperature of nine degrees is much greater than that in the effect of the Double-Bar allele. If the effect of the genetic difference is taken as the difference between the eye size in the two stocks at any one temperature, it is obviously greater at 16° C. than at 25° C. (Fig. 62). If the effect of the environmental difference of 9° (not the total environmental effect) is regarded as the difference in eye size at the two temperatures in any one stock, it is clearly greater for the Bar stock than for the Double-Bar stock. Then, of the difference between the largest eyes (Bar at 16°) and the smallest (Double-Bar at 25°), there is no single answer as to the relative potency of genes and environment. At 16° the genes have it; at 25° the major role is that of the temperature difference. For every combination of each environmental change and each genotype, the relative potency must be assessed individually.

These examples throw the emphasis back on the biochemical chain-reactions which lie between genotype and pheno-

type. The greater our knowledge of these becomes, the more readily we can correct for genetic inadequacy by appropriate environmental change. It is a simple matter to feed salts of iodine in correct dosage to those who need it, or to step up resistance to a disease in susceptible genotypes by vaccination

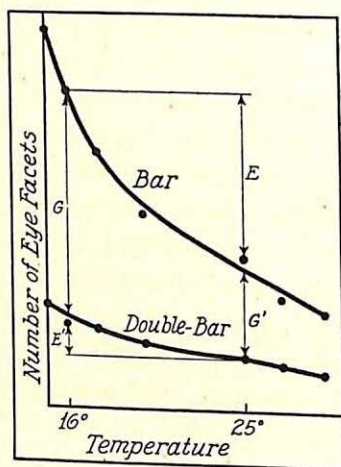


FIG. 62. Diagram showing the change in the eye size of Bar and Double-Bar *Drosophila* with changing temperature. E = change due to shift of 9° C. in Bar; E' = change due to shift of 9° C. in Double-Bar; G = difference due to genotype at 16° C.; G' = difference due to genotype at 25° C. (From data of Kraflka)

or serum treatment. This should make it clear that *artificial selection and environmental control are, after all, not alternatives between which we must choose*. The former is a treatment applied to the genetic pattern of a population. The latter is a treatment applied to the phenotype of an individual. Both can be used in the same instance, and the advisability of applying them should be considered separately.

The efficacy of eugenic measures is not the issue just here. What is pertinent is the constant possibility that, by acquiring sufficient knowledge of the way in which a trait develops, we can achieve control over it. To say that hemophilia and Huntington's chorea are hereditary diseases does not

mean that they are incurable. It simply means that our research on them should be directed into channels other than those of bacteriology.

We need to learn more completely the susceptibility of each trait to environmental modification. We need to learn what factors are normally variable, how much, and when. In our search for limiting factors, we must distinguish more carefully between uterine environment, familial environment, and general social environment.

It would appear well-nigh impossible to secure a sufficiently homogeneous environment for the study of the effects of genetic differences in man. Even with our experimental animals the problem causes constant difficulty. Only the uterine environment and those characters which complete their development within it offer some hope. The principal variations in the uterine environment are nutritive, and the similarity of the rat's nutritive requirements to ours, and the high degree of genetic homogeneity in the rat stocks now used for experiments afford a substitute for experimentation upon ourselves. Yet the accompanying list of the nutritive substances (Table III, p. 216) known to be limiting factors is extensive, and their combinations would be practically limitless.

Fortunately, nature has furnished us another means of isolating the effects of heredity and environment. Although it is impossible to hope for completely identical or absolutely different environments, or for completely different heredities, we can obtain identical heredities. Identical twins have developed from the same original zygote. Their genotype being identical in all respects, any differences between them must be due to environmental factors. The converse, however, that their similarities are entirely due to their genetic identity, is an error we should beware of, for they have also experienced the same uterine environment;²² generally they have

²² Just what differences can exist in the uterine environment is clear from the fact that "Mongolian" idiocy, which is perhaps a Mendelian recessive, finds expression principally in infants born very late in the mother's childbearing period. In other words, the conditions within the same womb

TABLE III

<i>Minerals</i>	<i>Vitamins</i>	<i>Amino Acids</i>
Calcium	A (or precursor carotene)	Cystine or methionine
Chlorine	B ₁ (thiamin)	Histidine
Copper	B ₂ (riboflavin)	Isoleucine
Iodine	avidin	Leucine
Iron	biotin (vitamin H)	Lysine
Magnesium	choline	Phenylalanine
Manganese	folic acid	Threonine
Phosphorus	inositol	Tryptophane
Potassium	nicotinic acid (pellagra	
Sodium	preventative)	
Sulfur	pantothenic acid	<i>Fats</i>
Zinc	para-amino benzoic acid	An unsaturated fatty
	B ₆ (pyridoxine)	acid (such as linoleic
	C (ascorbic acid)	acid) (vitamin F?)
	D (calciferol)	
	E (antisterility)	
	K (antihemorrhagic)	
	L ₁ , L ₂ (liver filtrate)	
	P (citrine)	

grown up together in the same family; and, being of the same age and sex, they are often inseparable companions, so that they fall naturally into as similar social environments as can be. What we really want to know is the answer to the question: How different can identical twins become after exposure to measurable differences of environment?

Of all the studies of identical sibs that have been made, few include any instances of their separation, particularly during the formative years. Some years ago Johannes Lange,

in a woman's prime and later when approaching menopause are sufficiently different to settle whether or not this affliction will manifest itself. As for identical twins, two or more other factors enter in. The fusion of their fetal blood vessels may result in inequalities in their nutrition. The asymmetry mechanism of the single individual is disturbed by its partition between the two, and a considerable frequency of mirror-imagery between one-egg twins is the consequence. Differences in position and pressure may also play some role. These several factors may be sufficiently potent to account for those slight differences in such characteristics as height, weight, head shape, and intelligence which even identical twins exhibit.

of Munich, made a very interesting study of twins with criminal records.²³ He examined thirty pairs of twins, in each of which one member had been imprisoned. Thirteen of these pairs were identical and seventeen were fraternal and like-sexed. Upon investigation, it turned out that in ten of the identical pairs the other twin had been imprisoned too; while in only two of the fraternal pairs was this true. Moreover, the case studies showed that in practically every instance the crimes committed by identical twins were similar in nature and arose from resemblances in talents, sexual tendencies, weak will, or alcoholism. The conclusion that crime is the unfortunate destiny of some individuals is weakened, however, when we consider once again the close similarity of the environments of two identical twins.

Among these twins there was one pair, the Schweizer twins, Ferdinand and Luitpold, who were reared apart from the age of eight under considerably different conditions. Luitpold received affection and good care, but showed himself irresponsible and ungrateful both toward his foster parents and at school and, later, in marital relations. Ferdinand was badly treated and severely disciplined by his foster parents, and did well in school. Then he ran away to his grandmother, who was hopelessly indulgent, and thereafter he showed himself completely irresponsible and immoral. Luitpold later married a woman of domineering will and energy who managed to keep him at regular work and away from bad companions, and under restraint he has become "goodnatured and tender, generous, and socially agreeable, popular, cheerful, and musical. As a husband he is most considerate. He is so sentimental that he often cries in church."²⁴ But withal his wife does not trust him. The brothers clearly share personalities very much alike, and require rigid discipline to supply the defects of their own weak will-power and irrespon-

²³ Lange, Johannes. *Crime and Destiny*. Boni Paper Books, New York, 1930.

²⁴ *Op. cit.*, pp. 162-163.

sibility. Evidently the differences in their environment have not created any marked difference in them in this respect, although their fate as adult citizens shows such a striking contrast. Yet we wonder about the common influences of their first eight years—are not these years, after all, the most important ones in the development of personality and character?

The most recent and extensive survey of our problem²⁵ is a summary of studies of fifty pairs of identical twins reared together, fifty pairs of like-sexed fraternal twins reared together, and nineteen pairs of identical twins reared apart. Of the latter, seventeen pairs were separated before eighteen months of age, one pair at three years, and one pair at six. The degree of separation ranged from complete to one in which the twins lived a few miles apart and attended the same high school for three years. Five judges rated the environmental differences as moderate for fifteen pairs, extreme only for four pairs.

When identical twins reared together are compared with those reared apart—a comparison suited to measure the potency of environmental differences—physical traits such as finger-ridge count, stature, head measures, and weight are found to be least affected by the environment; intelligence, somewhat more; educational achievement, still more; and personality or temperament, most of all. Of course, to some extent this seriation is due to the fact that our measures of these traits become less valid in the same order. Yet it is significant that the estimated degrees of difference in the environments were found to be strongly correlated with the scores of the twins. For example, estimated differences in schooling were correlated with measures of educational achievement to the extent of .91; differences in schooling were correlated with intelligence somewhat less.

When identical twins reared together are compared with

²⁵ Newman, H. H., Freeman, F. N., and Holzinger, K. J. *Twins: A Study of Heredity and Environment*. University of Chicago Press, 1937.

fraternal twins reared together—this time the potency of hereditary differences is being measured—the greatest differences are found in the physical traits, and the seriation is as in the preceding comparison but reversed in order. The relative potencies of heredity and environment in the two sets of comparisons are in fact just the reciprocals of each other. This means that we can never find a fixed ratio that will apply either to all traits or to all conditions. It is only possible to determine the degree of difference that a single change in an otherwise common environment can make in a particular trait developing in a particular genotype. It would be possible, for instance, to take the Dionne quintuplets—who are almost certainly identical—and in their otherwise remarkably similar environments determine the effect of supplying some of them, but not the others, with an excess of vitamins A, B₁, C, and D (or any four) as compared with the amount the average child gets. Any finding, however, would be true only for their particular genotype and their “standard” environment; and the experiments would need to be repeated on many sets of identical sibs before valid generalizations could be drawn. This is a dream for some utopia, where all identical sibs would, because of their unique value to society, be reared as wards of the state.

Meanwhile our study suggests that the relative potencies of heredity and environment depend largely on the comparative magnitude of the genetic and environmental differences in each particular situation. When the genetic difference is large and the environments are similar, the genes are mainly responsible for the result. When the genetic difference is slight and the environmental large, the influence of the latter predominates. No doubt this is a truism. Yet by continuing such studies until far larger numbers of cases have been collected, we may at last arrive at a statistically reliable estimate of the extent to which our various environments, as they are, contribute to the nongenetic differences of our population. And this will surely be worth while.

This chapter has dealt solely with the inextricable character of the roles of genes and extrinsic factors in the course of development. It now remains for us to trace that course, reading into it, as we go along, this biochemical and biophysical substratum we have just reviewed.



CHAPTER V

From Potentialities to Realization

BEFORE launching into the complexities of human development, certain general principles that will aid in understanding its character need to be made clear. In the first place, development is a progress toward greater effectiveness, brought about through an increase in the number of associated life-units and by a division of labor among them. Concomitantly, their mutual dependence increases. They must submit to a loss of independence in order to become welded into an *organism*. The several steps in this process include (1) growth, through an increase in cell number by mitosis; (2) cell movements, important in modifying form and organization; (3) cell differentiation and specialization, leading to the production of *tissues*; (4) the combination of tissues into *organs*; and (5) the correlation of parts and their integration into a working organism.

As pointed out in Chapter IV, the course of development is determined by the interactions of genes with one another and with their cytoplasmic environment, which is in turn subject to the stimulation of the external environment. Now in the course of development there is instance after instance where foresight appears to be exercised. Structures develop ahead of the need for them; they have reached a functional level before there is a demand for their functioning. Eyes develop in the total darkness of the mother's womb, hands and feet attain their form and structure before manipulation

or support are needed, kidneys develop while wastes are still effectively disposed of otherwise, and lungs are ready for breathing air at birth, although of no use beforehand. How can this be explained without attributing foresight to mere chemical substances, assuredly all that genes are?

Genes, it may be recalled, are subject to mutation, and the majority of all mutations are detrimental. Sufficiently damaging changes weed themselves out; their possessors never reach maturity, never leave offspring. Even less deleterious changes, if they lower viability or fertility, will in time disappear from the population, or be held to a low frequency. The result, as Charles Darwin pointed out in *The Origin of Species by Natural Selection*, is that hereditary types which show superior adaptation to their environments will tend to survive. In modern terms, most of the genes present at any given time in the individuals of a species are those that have stood the test of natural selection throughout numberless generations. Only such systems of genes as would lead to the complete development of mature individuals, capable of producing offspring, would ever be able to insure their own continuance. All others become extinct. The adaptive character of life is therefore to be explained neither by an inheritance of acquired characteristics nor by the foresight of gene-molecules; it is the product of natural selection. Nevertheless, the semblance of foresight in development is there, a semblance of plan and purpose. Only by keeping the action of natural selection constantly in mind is it possible to avoid teleology.

A corollary of evolution by mutation and natural selection is that related species possess a common fund of genes, in addition to those other genes which differentiate them. The more closely related the species are, the more genes they will possess in common. In terms of development, this means that all organisms of common ancestry start their development in much the same way. The developmental patterns of the remotely related diverge first, those of the closely related

remain parallel up to late stages. Conversely, we recognize these similarities in structural and developmental pattern—these *homologies*, as they are called—as evidences of common ancestry.

All related organisms tend to pass through similar levels of complexity in organization. However, since mutations are not limited in their effects to adult stages, the larval or embryonic stages may also come to differ. Only those aspects of development upon which vital later steps depend are so fundamental that any gross modification of them would necessarily prove fatal. In spite of the modifications, then, the general levels of organization through which related organisms pass in the course of their development are recognizably similar. Development may be likened to a great highway upon which all organisms start out together. The highway forks into roads, the roads into paths, the paths into faint trails. First in crowds, then in smaller groups, and finally one by one, the other organisms leave us. Some wander off up other routes of specialization than ours. Others halt at some particular stage of the journey, making only minor specialized adaptations for carrying on their lives successfully at this level of development.

The latter types have long been of profound interest to biologists. A series representing the major levels of animal organization customarily forms the backbone of courses in zoology. The *Ameba*, the *Hydra*, the flatworm *Planaria* and the roundworm *Ascaris*, the common earthworm *Lumbricus*, and—among chordates and vertebrates—the lancelet *Amphioxus*, the lamprey, the dogfish and the frog, the reptile (or the chick) and the cat—these form a classical series exemplifying different levels of organization from one-celled protozoan to mammal. When it was discovered, in the last century, that man and other mammals in their individual development pass through a similar series of developmental levels, the study of these types became of added interest.

It is, of course, true that none of these modern forms rep-

resents exactly either a level of our own development or any particular ancestor in our human lineage. Nevertheless, a study of their more general features will serve to clarify many peculiarities of our own course of development. Whatever develops at a more complex level is necessarily a modification of the organization characteristic of the simpler level. As a consequence, some structures appearing during development seem to be entirely useless—merely “reminiscent of ancestral conditions”; certain other parts, of use to the embryo, are later replaced by more effective organs in the adult. Structures of both these types may either disappear or may persist throughout life as vestigial organs. Nearly two hundred of the latter have been listed for man. Organs of a third group abandon their ancestral function, are retained in the adult either with or without modification, and acquire new functions.

Since the ancestors of the human species are extinct, we are forced to rely on these modern forms to illustrate the effectiveness as well as the limitations of the particular levels of organization characteristic of our own individual development. At appropriate points, then, these forms will be introduced for the sake of comparison, in the belief that such studies are of real value in enabling us to understand the character of human development.

CLEAVAGE—CELL MULTIPLICATION

The earliest phase of growth and development does not itself result in any division of labor—not, at least, in any that is visible. But it does lay the groundwork for a future division of labor. Repeated cell divisions result in a multiplication of the units (cells), prerequisite to any elaborate division of labor. As long as the individual is comprised of only one cell, the zygote, this one cell must carry on all the essential life activities. The more cells an individual becomes divided into, the greater the potentiality for specialization.

The principle works out just as it does in human society. An isolated man must carry on all his essential activities by himself, and these take so much of his time and effort that he has little left for nonessentials. In larger, yet still isolated communities, the division of labor can be carried out to some extent. Finally, a national or international group, with its highly specialized division of labor, has such efficiency that all essentials can be cared for by the labor of a minority.

Cell division during development is regularly mitotic. Mitosis provides every cell with chromosomes which are duplicates of those in the parent cells. Every cell thus gets its full diploid quota of genes, made up of the set originally brought in by the sperm and the set present in the egg. No matter how different the various body cells come to be through specialization, they are, with rare exceptions, all alike in their genes. They have the same hereditary pattern, a likeness which is the foundation of coordination among them.

This fact raises a serious problem, however. If all the cells carry the same genes, what makes them develop differently, one becoming a muscle cell, another a brain cell, another a liver cell, and so on? This question represents one of the major unsolved problems of embryology. The answer, as considered in Chapter IV, appears to lie in the interaction of the genes with their environment. The genes alter the characteristics of the cytoplasm, and localized differences in the cytoplasm then control the further action of the genes. For example, some of the pigment-producing genes act earlier than others during development. The secondary enzymes they produce may be so localized in the cell that a later cell division will distribute them very unequally to the new cells.

There is clear evidence that this happens. Materials, especially the stored food (yolk), are unequally distributed in the egg. The nucleus and most of the cytoplasm are at one end (the *animal* pole) and the yolk is at the other (the *vegetal* pole). When the egg is maturing, the cells

produced are very unequal in size, as you may recall. This is because the spindle is oriented perpendicularly to the surface of the egg, and the cell formed at the outer end of the spindle is cut off with just a nucleus and a little cytoplasm. It is a polar body. Such a division results in keeping all the stored food, so necessary for the growth of the embryo, in one

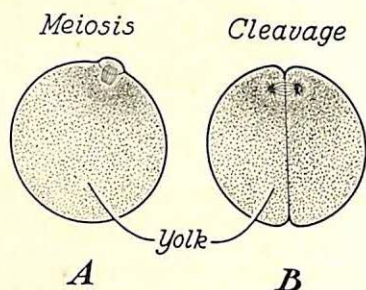


FIG. 63. Characteristic orientation of the spindle in eggs. A, at meiosis; B, at the beginning of cleavage.

cell. At the beginning of embryonic growth, however, the problem is quite a different one. Each of the early cells requires an adequate share of stored food and other substances. In eggs with a small or moderate amount of yolk, the first spindle is ordinarily oriented parallel to the cell surface, and the plane of division thus passes from animal pole to vegetal pole, effecting an equal division (Fig. 63).

The plane of the second division also runs from the animal pole to the vegetal, but at right angles to the first. The plane of the third division is at right angles to the first two, which means that it is approximately equatorial. These three divisions produce eight cells (Fig. 64).

Cleavage continues, with the cells becoming smaller and smaller, until, after six or seven successive divisions, the human embryo is a little ball of tiny cells, all together no larger than the one original cell. Up to this point there has been practically no growth—that commences later. Cleavage has merely portioned out the various substances present in the egg. The divisions have been leisurely, four to twelve

hours apart, so that the berry-like embryo is now, about two days old.

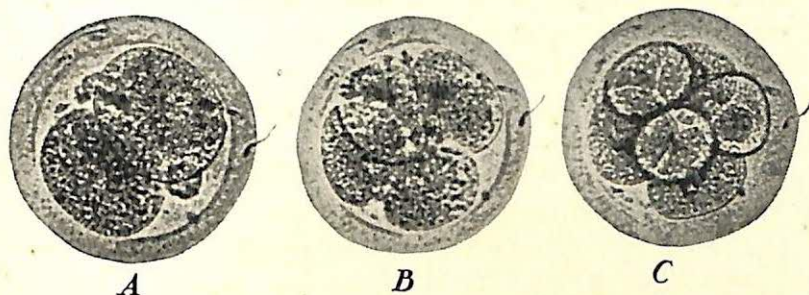


FIG. 64. Cleavage of the living monkey ovum (photomicrographs by Lewis and Hartmann; magnification about 180 diameters). *A*, two-celled stage (30 hours after ovulation), showing polar bodies and unsuccessful sperms. *B*, four-celled stage (38 hours after ovulation). *C*, eight-celled stage (50 hours after ovulation). (From Arey's *Developmental Anatomy*. Courtesy of W. B. Saunders Company)

At some stage in this process, as we know from other animals, the cells begin to lose their independence. This may be earlier in one species, later in another. It can be demonstrated in a simple way. If the cells are separated from one another, either experimentally or accidentally, while there are still just a few (four or even more), each of these isolated cells possesses all that is necessary to go ahead and develop into a complete individual. Since all such isolated cells that originate from a single zygote carry identical hereditary patterns, they develop into individuals that differ only by reason of exposure to varying environmental conditions. They are identical twins, triplets, quadruplets, or quintuplets, depending upon the number of isolated and surviving cells. Some time later, however, separation of the zygote into single cells, or even into groups of cells, will result in only partial development. Half-embryos and other monsters arise, struggle along for a while—then perish. *The parts of the embryo have become dependent upon one another and, when separated, cannot supply their respective deficiencies.* The prod-

ucts of some of the early-acting genes have already been localized, and it is too late to begin over.

In short, even before there is any visible differentiation among the cells, there are clear signs that they are no longer independent of one another. They have acquired different potentialities. The division of labor, though as yet invisible, has begun.

This may be illustrated among some of the more lowly organisms, which never get beyond these early stages in development. In Chapter I we traced the increasing division of labor in the green algae of the Volvox family. There we saw that, as the number of cells in the cell cluster or colony increases, they lose their independence. First, their freedom of movement is sacrificed; then, by division of labor, some become solely vegetative (*somatic*) cells, others retain the capacity to reproduce.

Cleavage further reinforces the nuclear control over the activities of the cytoplasm. Since by cell division the nucleus is multiplied many fold, while the cytoplasm remains practically the same in volume during cleavage, the ratio of cytoplasm to nuclear material in each cell drops tremendously (from about 400 : 1 to about 7 : 1).

Finally, there has been a tremendous increase in the proportion of surface to volume, for the volume is still what it was to begin with, but each of the several hundred tiny cells in the embryo now has a full surface of its own. Let us not forget that the surface of a cell, its membrane, in other words, is the gateway through which all substances enter or leave the cell. The volume, on the other hand, represents the amount of living substance which must be nourished. The relation between them is, therefore, of enormous importance, as we have already seen in our study of mitosis. Since, during the growth of a cell, its volume increases very much faster than its surface, the cell must soon reach a limit at which its membrane cannot transmit substances fast enough to maintain the protoplasm within.

Various solutions to this problem have been found. Irregularities in the shape of cells are quite general and increase the surface area without changing the volume. An ameba, with its irregular shape, furnishes a good example. On the other hand, permanent shape and more or less streamlined form are necessary for rapid locomotion, and a groove or two are the only increases of surface that such speedy one-celled organisms as *Paramecium* are provided with. A few one-celled plants, able to get along without much movement, have solved the difficulty by acquiring a shape in which all their protoplasm is spread in a thin layer about a great cavity filled with sap. These are the largest of all cells, aside from yolk-crammed eggs—but the shape has its disadvantages.

By far the most general outcome of the surface-volume problem is cell division. It may be combined with any of the previously mentioned devices, for many cells in complex organisms are very irregular in shape—nerve cells, for example—while plant cells are quite generally hollow, with a thin rim of protoplasm around a great vacuole full of cell sap. But the principal advantage secured by cell division—the multiplication into distinct units varying in their content of localized substances and hence capable of diverse specialization—makes it the nearly universal basis of growth, as we have found it to be of reproduction.

GROWTH BEGINS—THE HOLLOW BALL

As the number of cells in the tiny spherical embryo continues to increase, and the cells consequently become smaller and smaller, some naturally are internal in position. These, to be sure, have no lack of food, for an adequate supply has been stored up for all. On the other hand, an internal position is unfavorable for access to oxygen, and would make difficulties in the elimination of wastes. Distribution *through* cells is difficult, relatively slow, and inefficient.

The next change in the mode of development provides a

solution for this difficulty. Almost from the beginning the inner cells begin to move outward and to assume more favorable locations near the surface of the sphere. (It is now called a *blastula*.)

This change has several consequences. In the first place, it leaves the center of the embryo hollow. The cavity is filled with fluid absorbed by the embryo from its surroundings as rapidly as it grows, and this fluid forms an admirable means for the distribution of materials, since diffusion and convection through it are far more rapid than in cytoplasm itself. In the second place, the movement of the inner cells produces an increase in the size of the ball. *Thus growth begins—with an outward movement of the inner cells produced by division, and a rapid imbibing of water to fill the middle vacancy.*

What is the advantage of this type of organization over that of the solid mulberry-like form? A more adequate provision of materials from the environment to the cells and a new inner fluid-filled cavity enabling distribution to take place on two surfaces instead of only one—yes, these are obvious, and *the capacity for further growth is itself dependent on them*; for, as we have seen, it is limited primarily by the ratio of surface to volume, that is, by the problem of distribution. The blastula is capable of further growth, more cells can be maintained, and there is a corresponding increase in the capacity for specialization.

We can see how this works out in *Volvox* (Fig. 7E), which is characteristic of the developmental level of the blastula. Each individual on the surface of the hollow ball, which attains the size of a pin's head, rather closely resembles the individuals making up the colonies of its simpler relatives (Fig. 65). Each has two whiplike flagella, and green chloroplasts enable it, like other plants, to synthesize its own food. Each cell is thus nutritively independent of all others in the group, but is bound to them by the jelly-like secreted capsule which makes up the envelope of the hollow ball. Moreover,

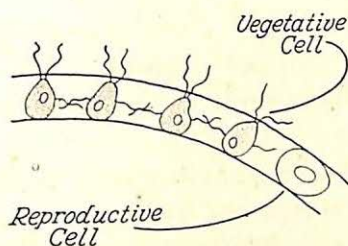


FIG. 65. Part of a globular *Volvox* colony, to show vegetative and reproductive cells.

each cell sends out projections which make contact with those of neighboring cells and enable communication to take place. We have already noted that the reproductive capacity is yet further restricted than in simpler relatives.

Here we can add coordination to the growing dependence and the correlative division of labor among the cells seen in the simpler members of this group of algae. The more fundamental life activities, nutrition, respiration, excretion, and distribution, we shall find, are surrendered to specialization last of all, and even then but incompletely. Every cell carries on a certain amount of this generalized metabolism. In the blastula itself there is no evidence of cell specialization at all.

At this level of organization, or earlier, we are forced to consider the question of individuality. Just when does the mutual dependence of associated cells become so great that we should cease thinking of them as separate individuals, and begin to consider them as units in a greater whole, the *organism*?

The change from a cluster or colony of individually complete units, as in the four-celled embryo or the simpler algae of the *Volvox* family, into an individual made up of specialized and mutually dependent cells, as in the blastula or *Volvox*, is a gradual one. To set at any particular point the transition between the colony of distinct individuals and the larger organism must be arbitrary. *Volvox*, for instance, we may consider equally well as a colony of one-celled algae or as an organism of relatively unspecialized cells.

There is a striking analogy between this situation and the relation between each of us and our social group. We insist on regarding ourselves as individuals, although human cultural development has long passed the stage when people were even moderately independent. Civilization, like all other kinds of development, has grown up partly through the greater efficiency proceeding from our specialization, through a division of labor among us. Our social system might thus be regarded as an organism itself, of which we are the units, while our cells, if they could think, might prefer to regard themselves as individuals in a society.

There are, to be sure, differences between the relation of our cells to us and our relation to human society, but are they as fundamental as we might at first suppose? Freedom of movement is one obvious difference. Yet cells are by no means always fixed in place. During development they move about a great deal, and even in maturity there are some that still do. The white blood cells rove over our entire body, through blood vessels and out of them, into the spaces between the cells, wherever their own nature and the stimuli to which they respond direct them.

Are we more free to follow our fancies? At least most of us know the force of economic limitations that tie us to our spheres of labor. While we exercise more or less choice in picking a vocation, we certainly are limited in this, too, by our innate ability, by our training, and by the availability of jobs, among other things. The distinction of free will becomes very tenuous as we examine it. Nor must we blindly conclude that all social groups resemble our own human societies. Ants and bees are social no less than ourselves, yet they are governed almost as completely in their behavior by their instincts (that is, ultimately, by their genes) as white blood cells are.

In our society, we, the members, are born and die, and others take our places while our social group lives on. So,

too, within our bodies, cells are formed, live, and perish, their places then to be filled by others, their work to be taken over, or, occasionally, to prove an irreparable loss. Human societies, too, have ended and will end quite as we die, or as an ant hill is wiped out by deluge or famine. From such parallels as these, the biologist is led to see that, just as each man and woman may be studied as a society of cells, so a social group may be considered as a higher organism. This is not the whole truth, to be sure. On each level of organization, new and as yet unpredictable qualities emerge. Nevertheless, just as a man's life activities are clarified and rendered intelligible through our knowledge of the cell, so too our understanding of the social "organism" should be based on our scientific study of lower hierarchies of organization. The biologist who knows his own dependence upon physics, chemistry, and mathematics is eager for a history that will portray man as at once the evolving creature and maker of his biological environment,¹ and for a view of our social problems that will take into account the biological laws of the organism.

An organism may be regarded as an organism because its units labor in harmony for the common good. The cells in our bodies carry a common genetic pattern which underlies the harmony of their behavior, to this end. The social organism has no genes and no mitosis. It must rely instead upon its culture pattern, acting in a thousand formative ways upon each newcomer to the group. In this realm at least, the transmission of acquired characteristics is a fact. We may, indeed, be thankful that it is, for it renders our culture pattern adaptable—far more susceptible to change than man's genetic pattern, which is essentially the same today as a hundred thousand years ago. But is the culture pattern strong enough to

¹ For an excellent development of this point of view by a historian, see *Progress and Power*, by Carl T. Becker, of Cornell University (Stanford University Press, 1936).

hold us, through education and tradition, to the required degree? Or is it in irresoluble conflict with our individual tendencies toward self-willed freedom and independence?

These are questions we cannot answer today. We can only say with Donald Culross Peattie that "biologically considered, man is the sole being who has its destiny in its hands. And few of his species feel any sense of social responsibility higher than the fundamental one of begetting children. Yet now and then, as the years pass, comes a Noguchi, Pasteur, Beethoven, Lincoln, Asoka, Marcus Aurelius, or Plato [or, we might add, a Christ]. They are humanity as it might be."²

THE HOLLOW BALL BECOMES A TWO-LAYERED SACK

The hollow ball or blastula is growing. Were we to watch the process in a simple egg containing relatively little yolk, we would soon see that this growth is uneven. The cells around the animal pole become more and more active, grow faster and faster. Those at the vegetal pole lag far behind and do not divide nearly so frequently. The ball consequently becomes more and more lopsided (see Fig. 66). As the cells from the animal pole expand, the cells from the vegetal pole become tucked up into the interior. These movements are kept up until the embryo is first cuplike and then, as the lips draw together, like a sack. (Such a process is called *invagination*, which means "pushing in to make a pocket.") The formation of the sacklike embryo, or *gastrula*, as it is called, is essentially the same in eggs which have yolk, except that the yolk is in the way of the formation of the pocket. In a frog's egg, which contains a moderate amount of yolk, the invagination takes place to one side of the yolk-filled cells of the vegetal pole; while in eggs with an enormous mass of yolk, such as a bird's, cleavage has been quite ineffective except in a little cap of cells at the animal pole, and the invagination takes

² Peattie, D. C. *An Almanac for Moderns*, p. 312. G. P. Putnam's Sons, New York, 1935.

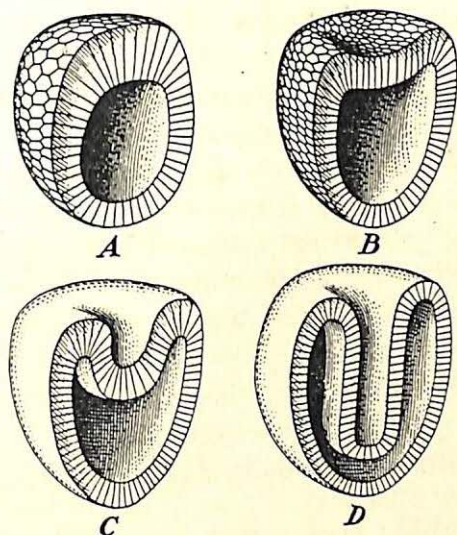


FIG. 66. Four stages of the invagination that transforms the hollow blastula into a sacklike gastrula, as seen in many animals. The embryos are represented as cut halves to show their interiors. Animal poles are at the bottom, vegetal at the top. (From Goldschmidt's *Ascaris*. Courtesy of Prentice-Hall, Inc.)

place at one side of this. In any event, the result is the same: *Two layers of cells are produced, an inner and an outer; and the embryo has acquired a cavity open to the exterior*, as shown in Fig. 66.

The outer layer, which we call the *ectoderm*, being exposed to the external environment, comprises those cells which become specialized to respond to various sorts of external stimulation and to coordinate the behavior of the organism. In other words, this means (1) the outer layer of the skin; (2) its products, such as our hair, nails, the enamel of our teeth, sweat, oil, and milk glands, and, in other animals, feathers and parts of scales; (3) major parts of the sense organs; and (4) the entire nervous system.

The inner layer, or *endoderm*, lines the new cavity with the opening to the exterior. This space is to become the digestive cavity. The endoderm consequently forms mainly

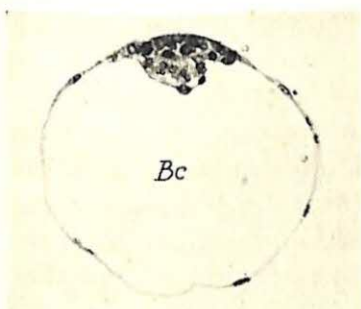
the inner layer of the digestive system, with cells specializing in secreting mucus or various digestive enzymes, or in absorbing the digested food. However, we shall see later that quite a number of other important organs grow from it as pouches or pockets. In birds' eggs, the endoderm, with the ectoderm on top of it, at first lies like a disk on top of the great ball of yolk. Gradually this disk will extend down over the surface of the yolk until finally it will completely enclose it, making what is known as the *yolk sack*. But this will take quite a while. In the meantime, the endoderm has already begun its work of digesting the yolk and transferring food to the overlying cells of the ectoderm.

Now in human embryos, and, of course, in other mammalian embryos likewise, there is very little stored yolk.³ Perhaps we should expect the human embryo to form first a blastula and then a gastrula, in the way a frog does, since the egg of the latter also has rather little yolk. However, this is not the course of our development. On the contrary, we develop in a manner reminiscent of a chick or lizard, and not like a frog—quite as though we carried a lot of yolk, or had once, and had never broken ourselves of still developing in the immemorial way.

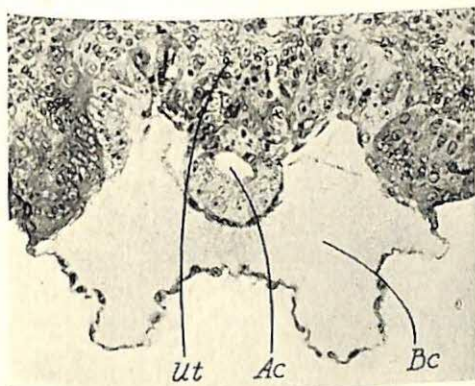
After we have reached the berry-like stage, it can be seen that we have a distinct outer layer of cells. This grows faster than the inner mass, opening up a cavity between them, the inner mass remaining attached to the outer layer at the animal pole (Fig. 67A). This stage is comparable to the blastula of a reptile or bird with its yolk removed.

Meanwhile, after a week or less of development, we have moved slowly down our mother's Fallopian tube, at the upper end of which we originated as zygotes by fertilization, and have now reached her *uterus* (womb). Here, at about

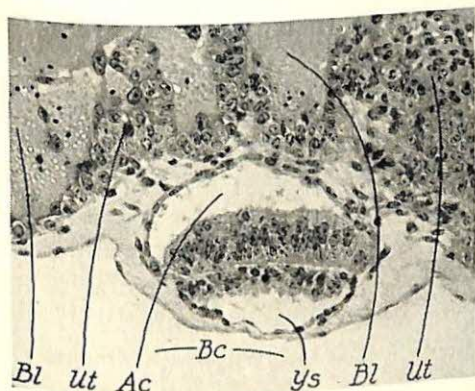
³ One might note here another instance of what is apparently foresight. The human embryo has need for only a little yolk, as it will shortly be supplied with food through a connection with its mother's body. The amount it stores as an egg is correlated with what it will need later.



A



B



C

FIG. 67. Sections through three stages in the early development of the rhesus monkey (*Macacus rhesus*), photomicrographs, magnification about 150 diameters. *A*, at nine days. A hollow sphere (blastocyst) with an inner cell mass at one pole; not yet implanted in the uterus. *B*, at ten days. Implantation has occurred, and the outer sphere has partially collapsed. The inner cell mass of ectoderm has become hollow, forming the amniotic cavity (*Ac*). Beneath the ectoderm appears the first thin sheet of endodermal cells. *C*, at thirteen days, showing only the immediate vicinity of the embryo proper. At *Ac*, the amniotic cavity; at *Ys*, the empty yolk sack; between them, the embryonic disk, made up of a layer of ectoderm (above) and a layer of endoderm (beneath). *Bc*, the cavity of the blastocyst; *Ut*, tissues of the uterine mucosa; *Bl*, blood lakes containing blood cells. (From Streeter and Heuser. Courtesy of Carnegie Institution of Washington)

our tenth day of existence, we become firmly implanted in the surface layer of the uterus, which has meanwhile grown a great deal thicker, and has acquired an extraordinarily rich blood supply. Finally we burrow into and are quite covered over by the growth of this surface layer of the uterus, the *uterine mucosa*. The inner cell mass lies buried deepest. Our bodies will form from this inner cell mass alone, and not from the outer sphere of cells, which serves another function. From the latter there shortly grow out little rootlike projections of cells, which imbed themselves deep in the mother's tissues. Meanwhile quite a large space has opened up in the uterine mucosa about us, a space connected with our mother's blood vessels and filled with nourishing blood. Very early we are thus bathed in a lake of blood, from which oxygen and dissolved foodstuffs (sugar, amino acids, and so forth) can diffuse into our own fluid-filled central cavity and body cells, while our wastes (carbon dioxide, urea, and so forth) will diffuse in the reverse direction, into our mother's blood.

At the time when we are becoming implanted in the maternal tissues, the inner mass of cells also becomes hollowed out, its tiny cavity surrounded by a layer of thin cells above and one of tall columnar cells below (Fig. 67B). The latter flatten out into a thick plate of cells, the embryonic disk from which our body proper will develop. The rest of the inner cell mass and hollow ball at this stage will go to make up the auxiliary structures needed for our nourishment, respiration, and waste disposal during the long months we spend within our mother's body. At about the time of implantation a thin layer, the endoderm, makes its appearance, also splitting off from the inner cell mass. It too grows thicker, platelike, and proceeds to separate into a thick upper layer next to the ectoderm, and a thin sheetlike lower layer which surrounds the imaginary yolk (Fig. 67C). At this stage of our development we correspond to the gastrula of a reptile or bird.

An animal which develops only to the level of the two-layered sack

Two great subdivisions, or *phyla*, of the animal kingdom comprise individuals who remain as adults at the developmental stage of the gastrula. One of these is the phylum of the sponges; but since they very peculiarly turn themselves completely inside out during their development, they can

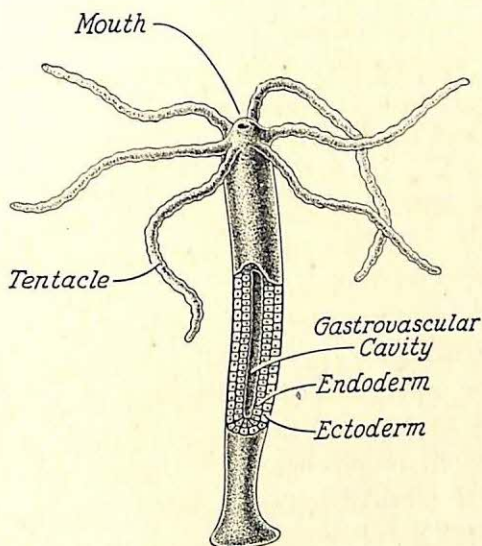


FIG. 68. The *Hydra*, a simple, fresh-water animal built on the plan of the two-layered sack. (Redrawn with modifications from Buchanan's *Elements of Biology*. Courtesy of Harper & Brothers)

hardly serve as a typical example. A better one is provided by the phylum of the coelenterates, which includes jellyfishes, sea anemones, corals, and, among others, the relatively simple fresh-water polyp, *Hydra* (Fig. 68).

The *Hydra* is, indeed, except for the crowning fringe of tentacles around the mouth, remarkably like a gastrula.⁴

⁴ The *Hydra*, it is true, does not attain its gastrula-like organization by invagination. The endoderm is formed from the ectoderm of the blastula by an inward movement of cells from the surface, thus providing a deeper layer beneath the ectoderm. Later, at the vegetal pole, an opening is formed.

These tentacles, too, are simply projections of the sack-like body. It is not in the general organization of the body that the *Hydra* surpasses the gastrula, but in the degree of specialization which the cells attain. Let us see just how effective a division of labor is possible among the cells when the body plan is simply that of two layers enclosing a cavity open at one end to the exterior.

The gastrovascular cavity, as it is called, is a very useful thing. Since it has an opening to the outside, food can be taken into it and partially digested there, relieving each cell of the necessity of entirely digesting its own food internally. Since every cell, too, has a surface exposed either to the outer fluid environment or to the inner, excretion and respiration are simple matters requiring no specialization beyond the mechanisms of the single cell. With these handled directly, and with currents in the central cavity supplying food to all parts, there is no need for special means of distribution. Specialization is correspondingly limited to the activities of nutrition, sensation, coordination, response, protection, and reproduction.

The provision of two layers, to begin with, enables the outer layer, in contact with the environment, to specialize in the functions of protection and food-getting, while the inner layer, exposed to the internal cavity, specializes in the various digestive functions. Besides this, both layers have certain kinds of specialized cells, adapted for sensation or coordination, or for movement.

In addition to all these, each layer has unspecialized cells from which the specialized cells develop. Such a cell in the ectoderm may *differentiate* into a sensory cell, or into a nerve cell, or into a stinging cell, or into a cell which is protective

Some biologists believe this is the more primitive mode of gastrula formation, and that invagination evolved later, as a developmental short cut. Be that as it may, the *Hydra* is clearly a two-layered sack when mature, and affords an excellent example of specialization on this level of organization.

at its outer end and contractile like a muscle cell at its inner end. A similar cell in the endoderm may differentiate into a gland cell which secretes slimy mucus and digestive enzymes; or into sensory or nerve cells; or into cells muscle-like at their bases and, at the other end, producing flagella that lash the food about in the central cavity, as well as pseudopods that engulf food, as does an ameba, for internal digestion.

Coordinated behavior arises from the fact that the nerve cells communicate with their neighbors by means of the branches which each extends out from its cell body. Thus over the whole organism there is a network of nerve cells, in contact with one another as well as with the sensory cells on the one hand and the muscle cells on the other. Yet there is nothing recognizable as a brain, nor even any provision for centralized control over behavior. Only around the mouth nerve cells are especially abundant.

Hydra reproduces both sexually and asexually. Sex organs are formed from the undifferentiated cells of the ectoderm at certain seasons of the year, and the same polyp may produce both eggs and sperms. The rest of the year the polyp simply puts out buds from its body. The unspecialized cells in a bud proceed to generate a new *Hydra*, mouth, tentacles, and all, its cavity at first communicating with that of the parent. Eventually the cavity is closed off, the tissues are pinched away from the parent's, and the offspring becomes independent.

The two-layered sack stage of development is evidently capable of considerable differentiation. Yet the radial symmetry, implying lack of a head and the absence of central nervous control, and the lack of any provision for internal transport have limited the behavior and the size of those animals which have retained this general plan of organization. Locomotion is slow and laborious, adaptability is slight, and life at all is possible only in an aqueous environment.

THE MIDDLE LAYER—PROVISION FOR SPECIALIZED DISTRIBUTION, EXCRETION, AND MOVEMENT

In our own development, we may recall, the gastrula stage is greatly modified. Nevertheless, there is a tiny canal through the ectoderm providing an opening from the digestive cavity. Stretching in one direction from this opening there forms a shallow groove in a narrow thickened band where ectoderm and endoderm meet and merge into undifferentiated tissue. This is the *primitive streak*. In the opposite direction runs another shallow groove in a thickened band of cells, which is the beginning of our central nervous system, forming just as it does in the frog.

If we were to watch a frog or salamander embryo developing within its transparent coat of jelly, we would see a great external change appearing not long after the gastrula was complete. At the lip of the opening into the central cavity a shallow groove appears, running forward toward what in the future will develop into the head. It lengthens and deepens; folds margin it, grow higher, curl over toward one another. At the head end, the trough is considerably broader. Behind this region the folds meet first; then, gradually, they fuse all the way in both directions (see Fig. 75). When done, this process has produced a tube extending along the back and ending in a bulb at the head. Thus, there originate from the ectoderm the spinal cord and brain, making up the central nervous system.

These two grooves, the primitive streak and the *neural groove*, between them mark out the primary axis of the body, from head to tail. In Chapter IV (pp. 192 f.), the formation of the organizer of the neural tube in the cells located at the dorsal lip of the pore of the gastrula was described. The primitive streak in the embryo of a mammal or bird is similarly located in relation to the neural tube, and experiments have shown that it produces the organizer of the neural

tube. It is therefore generally regarded as a structure homologous to the dorsal lip of the pore of the gastrula, although superficially it looks very different.

Another important thing about the primitive streak is that from it on either side there begins to arise a third layer of cells (Fig. 69). This lies between the ectoderm and the endoderm. It is the *mesoderm*, which provides most of the bulk of our body, for from it come muscles and bone, cartilage and

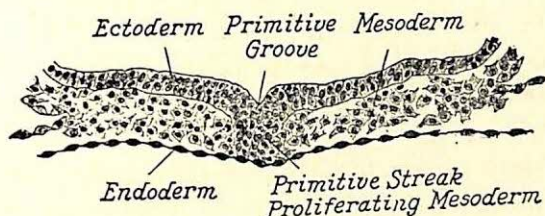


FIG. 69. A transverse slice across a human embryo, showing how the mesoderm grows from the primitive streak. Note that the cells in the three layers are already different in character. Magnified about 150 diameters. (From Arey's *Developmental Anatomy*, after Streeter. Courtesy of W. B. Saunders Company)

connective tissues, heart, blood vessels and blood, kidneys, reproductive organs, and the deeper layer of our skin.

An animal which gets no farther in general development than mesoderm formation

Under stones in our streams and ponds there may often be found numbers of small flatworms (Fig. 70), each gliding smoothly over the rock like a snail. Unlike *Hydra* and its relatives, this creature obviously has a head, with a couple of projecting lobes on the sides and two eyes, appearing rather crossed, between them.

A line drawn from the tip of the snout to the tip of the tail would divide this animal into two halves, each side a mirror-image of the other. In other words, the flatworm is *bilaterally symmetrical*. As a consequence, it has a front end, a "head," and the sensory organs tend to be concentrated

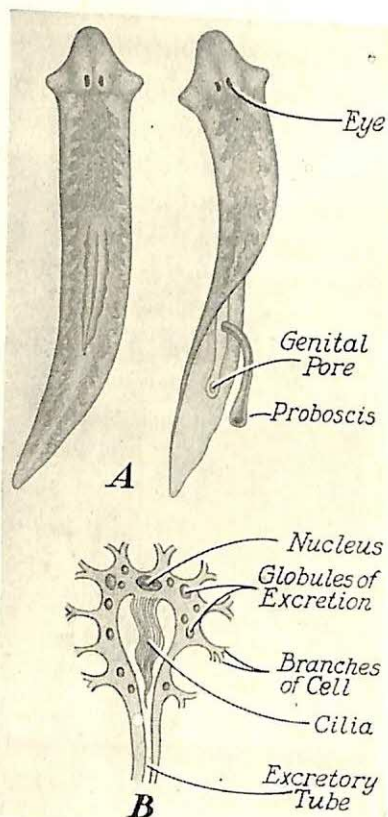


FIG. 70. A, *Planaria*, a flatworm. B, one of the flatworm's excretory, or "flame," cells. (Redrawn with modifications from Guyer's *Animal Biology*, ed. 2. Courtesy of Harper & Brothers)

here where the animal can be informed most promptly of its approach toward food or danger as it moves forward.

Examining its internal organization, we notice that it has a well-developed intermediate layer between the ectoderm and endoderm. The cells of this mesoderm are differentiated, in the first place, into muscle cells, which enable the animal to contract, change its shape, or turn to right or left. (Its smooth, gliding motion, however, comes from cilia growing on the under surface, which beat in a film of mucus produced by gland cells, also on the under surface. Like a cater-

pillar tractor, the flatworm thus supplies its own roadway.) Some of the muscles encircle a portion of the digestive cavity near the mouth, thus forming a pharynx, useful for sucking in the food.

Other cells in the mesoderm specialize for excretion; for where there is mesoderm, there are cells away from the surface of the body, for the disposal of whose wastes special provision must be made. These special excretory cells lie at the ends of a branching system of tubes which communicates with the external surface of the worm. Each one of these cells has a big tuft of cilia flickering like a flame in the duct, and thus producing currents that sweep the wastes down the ducts and out of the body. (For this reason they are called "flame cells.") Opposite the "flame," each excretory cell has numerous branches which project among the other cells of the mesoderm and into the spaces between them, and there collect the wastes.

Most of the mesoderm cells, however, are unspecialized. They assist in the distribution of materials, and at least many of them can at need turn into the various kinds of specialized cells. Because of this, if we cut a flatworm into bits, each part will be able to regenerate what it lacks, and can develop into a perfect individual.

There is also considerably more advanced specialization in ectoderm and endoderm than in *Hydra*. There are various kinds of sensory cells, taste is present, and the simple eyes we have already mentioned provide a response to light, although they cannot form an image. The nerve cells are organized into two long chains, with cross-connections like the rungs of a ladder; and between the eyes there are large masses of nerve cells. These *ganglia*, as they are called, forecast by their position the brain of higher animals.

The digestive cavity is a sack lined with endoderm, as in *Hydra*. Sometimes the mouth is at the snout. More frequently it is in the middle of the underside (see *proboscis*), and the digestive cavity branches to all parts of the body, as-

sisting in the growing problem of internal distribution of materials.

Reproductive organs of both sexes develop in each flatworm, as in the polyps. They are really the most specialized of all the systems. There are numerous *testes*, which produce sperms, at the ends of a branching system of ducts that leads to the *penis* and *genital pore*. There is also a pair of *ovaries*, which produce eggs, at the ends of long ducts into which open numerous yolk and shell glands; and there is a pouch into which the penis of another worm enters for the transfer of sperms. It is worth noticing that even hermaphroditic animals like the flatworm rarely fertilize their own eggs. Just as with us, inbreeding would result in the homozygous condition of any recessive genes, and most of these, as we know from many organisms, if not from the flatworm, are harmful.

To sum up, a flatworm is far closer to our type of organization than a polyp is. Its main advances are: (1) bilateral symmetry, including an emergent head; (2) mesoderm, including specialized excretory and muscle cells; (3) a cordlike nervous system running the length of the body, with an indication of a brain. Life on this level of development has already become surprisingly complex.

THE MEMBRANES OF THE EMBRYO—EARLY PROVISION
FOR OUR NOURISHMENT, RESPIRATION, EXCRETION,
AND PROTECTION

We have seen how, as embryos, we became imbedded in the lining, or mucosa, of our mother's uterus, and how our outer layer of cells proceeded to send out rootlike growths into the maternal tissues. This thin outer layer is soon strengthened by the addition of a layer of mesoderm. This in turn separates into two layers, an outer layer that lies against the ectoderm, and an inner layer that lies against the endoderm. The large cavity between the outer layer and the embryo proper is eventually completely lined with meso-

derm. In this fluid-filled cavity, the *coelom*, the embryo and its yolk sack dangle from the outer sphere by means of the body stalk (Fig. 71).

The outer layer formed in this fashion by the fusion of ectoderm and mesoderm is the *chorion*. It not only serves to protect and anchor us, but acts as the primary organ which

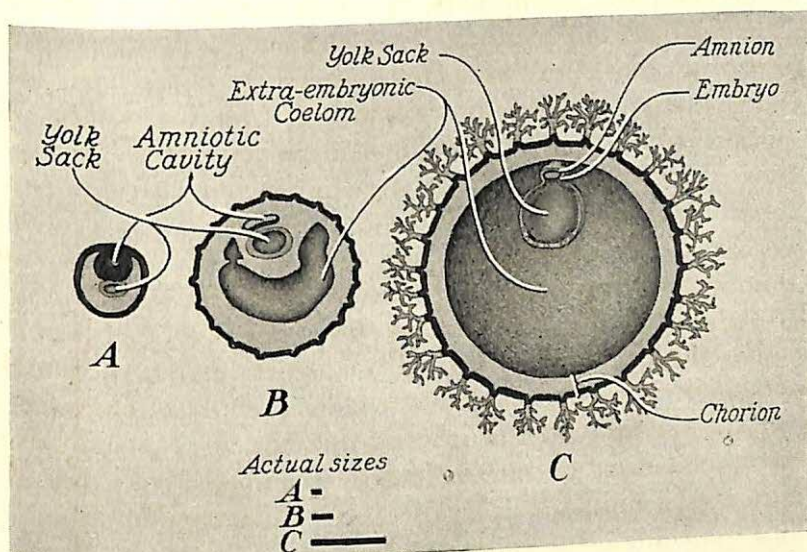


FIG. 71. Diagrammatic cross sections through early human embryos, together with their membranes. *A*, at approximately twelve days old. Amniotic cavity and yolk sack are present. *B*, at approximately fifteen days old. Villi are just beginning to grow out from the chorion. *C*, at approximately twenty days old. The villi are well developed all over the surface of the chorion. Tissues: ectoderm, black; endoderm, medium gray; mesoderm, pale gray.

cares for our embryonic nourishment, respiration, and disposal of wastes, through exchange with the mother's blood to which it is exposed. Later a large part of the chorion contributes toward the formation of the *placenta* (see p. 252).

Within the inner mass of ectoderm a small cavity also appears, at the age of about ten days. This rapidly increases in size, and lengthens as the embryo does. The walls and roof thin out to a mere membrane, ectoderm on the inside, meso-

derm outside, remaining attached only at the hind end to the chorion above. This membrane is the *amnion*, and its attachment to the chorion is the body stalk, a forerunner of the *umbilical cord* which runs from our navel to the placenta. The cavity of the amnion fills up with a fluid, clear and watery, and this cradles our developing body, which forms the floor of the cavity.

In reptiles and birds the amnion and chorion arise as a fold of the body wall extending all around the embryo, and then growing up and over until it meets on top of the embryo and encloses it. In our development the same end is attained by the appearance and enlargement of one cavity in the inner mass of ectoderm, and of another in the mesoderm. Here is an example where our development has effected a short cut and become more straightforward when compared with egg-laying animals.

Next to the chorion is the great cavity (or coelom), completely lined by mesoderm. In the lower animals, as in roundworms⁵ or segmented worms, for instance, such a cavity is of great value. In roundworms, which have no circulatory system, the coelom provides an easy channel for the distribution of dissolved foodstuffs and gases (oxygen and carbon dioxide). In both roundworms and segmented worms it serves in the collection and disposal of wastes. For us, as for the other higher vertebrates, most of this cavity lies outside the embryo proper and is gradually eliminated by the enlargement of the amnion. As for the part that is left within the body after the side walls of the body grow down and enclose the gut, what with our elaborate circulation and our highly efficient lungs and kidneys, there is little more function left for it than to provide a space where such organs as lungs, heart, and stomach may expand and contract.

The endoderm, now covered with a layer of mesoderm

⁵ The zoologist may object that the body cavity in roundworms is not a true coelom. It has no inner layer of mesoderm. Functionally, however, it plays the same role. For a popular study of biology based on the roundworm see *Ascaris*, by Richard Goldschmidt (Prentice-Hall, New York, 1937).

which will later provide muscles for moving food through the digestive tube, lengthens out into a hollow gut, quite empty. Strangely enough, the lower part of this gut continues to grow out as a sack enclosing an imaginary mass of yolk, and, at the age of three and one-half weeks, is approximately as large as the whole body of the embryo (Fig. 72).

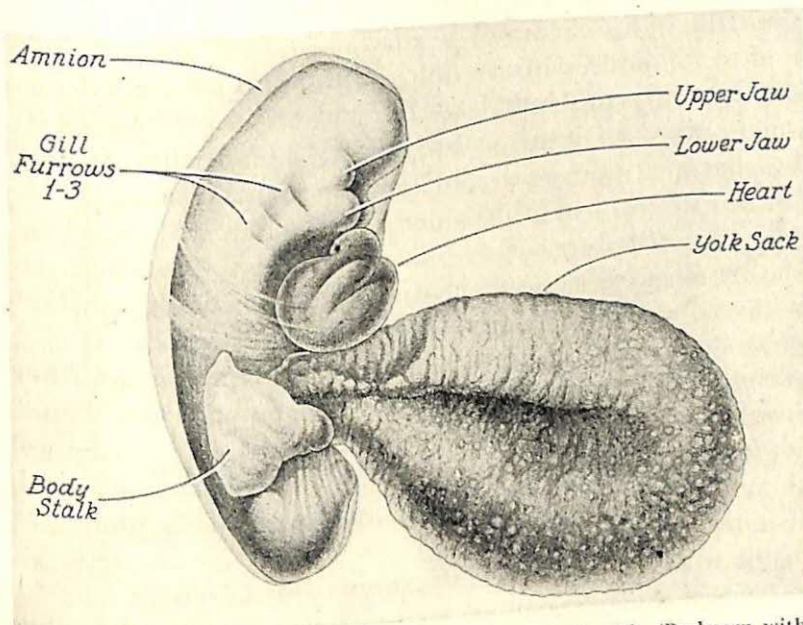


FIG. 72. Human embryo about three and one-half weeks old. (Redrawn with modifications from Arey's *Developmental Anatomy*, after His. Courtesy of W. B. Saunders Company)

After reaching a maximum size at six weeks, the yolk sack stops growing and becomes smaller and smaller in proportion to the rest of the body. Finally it is gathered into the umbilical cord, the scar of which is the navel. Could any better example of the uselessness of certain features of our development be offered? Why do we continue to produce a structure whose value we can explain only in terms of its usefulness to animals which develop from eggs containing a lot of yolk—fishes, frogs, reptiles, and birds? Why have we genes, to put

it in other terms, which regulate our development along lines suitable not to our condition but to that of more primitive forms? Why, if not that along with our characteristically "human" genes we have others we might better call "fish" or "reptile" genes?

This is not an isolated example. The very next structure to be discussed presents similar features, and we shall run into many more examples of a lack of straightforward development. Before we are so much as three weeks old, another sack begins to protrude from our gut behind the yolk sack, and to grow up into the body stalk. This is the *allantois*. Two large arteries and a big vein accompany it and grow on into the chorion. Here the blood coursing through the arteries is distributed into branches running down into the rootlike projections of the chorion, and thence into a myriad of exceedingly tiny, microscopic vessels with very thin walls, called *capillaries*. From these it is gathered into branches of the big vein, and so goes back toward the heart. While these blood vessels play an important part in carrying on the necessary exchange of food, oxygen, and wastes between us and our mother's blood, the allantois itself gradually dwindles away.

When we are between six and seven weeks old the *cloaca*, that part of the gut behind the junction of the intestine and allantois, undergoes a startling change. The wedge of tissue in the anterior angle of the junction commences to push rearward all the way to the body surface, until the cloaca is split into two portions that will later open to the exterior separately. Ducts from the kidneys and reproductive organs grow down and open into the part connected with the allantois, and after birth this modified portion of the cloaca functions as our *urinary bladder*.

This roundabout way of developing a bladder seems quite inexplicable until we turn for enlightenment to the birds and reptiles. Animals which develop on land within eggs require, just as much as the rest of us, some means of breath-

ing and disposing of wastes before they hatch. How does a chick breathe when inside an egg? We know enough already to realize that a large surface will need to be exposed, if the exchange of gases is to be adequate. How is this provided? The answer is—the allantois. This bladder, with its great blood vessels, grows until it fills all the space between the amnion and chorion. It fuses with the latter and, thus, comes to lie just under the shell, exposing the blood to the air over as large an area as possible. Moreover, the protein wastes of the body can be deposited in the allantois where they will do no harm to the developing embryo. Later, quite as in our development, the cloaca is partitioned and the allantoic part serves in adulthood as the urinary bladder. But in the primitive fishes and the amphibia the cloaca is never divided. The urine, the reproductive cells, and the waste fecal matter mingle there, and are voided through a common opening.

Here again we have run into a phase of our development which we can interpret only in terms of usefulness to more primitive forms of life. It is as though we had started our development under the delusion that we were to pass through it like a chick, and then suddenly came to a realization that instead we were sheltered within our mother's womb, and had to readapt ourselves as efficiently as possible to new modes of securing food and oxygen and of disposing of wastes. This, of course, cannot be so. There is no conscious, but rather a purely automatic, control over development. *Then why does our genetic pattern shape our development along lines useless and inefficient to us, though of value to more primitive animals?* It can only be, as pointed out in the introduction to this chapter, that our present genetic pattern is a modification of a less advanced ancestral pattern that was adapted to different conditions. In spite of all its marvelous adaptation to life and growth within the uterus, our development manifestly shows that these features are but superimposed on the ancient status of the yolk-crammed egg laid and then left to its own resources.

The amnion later swells tremendously, filling all the available space between our chorion and our body. Around the body stalk and yolk sack it forms a sheath, binding them together into the umbilical cord (Fig. 73). Meanwhile the outer half of the chorion has become quite bald, the rootlike growths continuing to develop only where, as we grow, they still

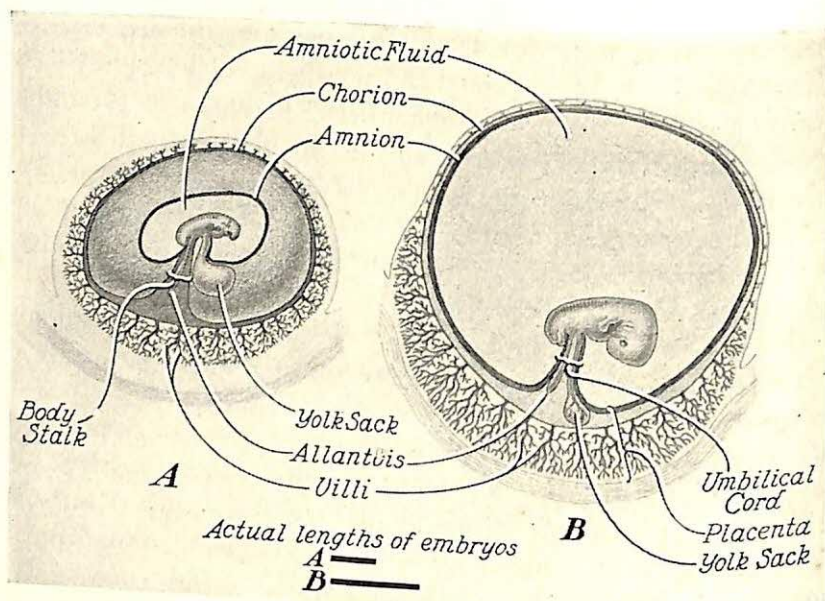


FIG. 73. Diagrams of human embryos with their membranes, to show how the enlargement of the amnion presses the yolk sack and body stalk together to form the umbilical cord. *A*, at about four weeks of age. *B*, at about six weeks of age.

remain in contact with the lining of the uterus. This area of contact is finally reduced to a platter-like structure made up of the branching growths from the chorion, the surrounding lakes of maternal blood, and the underlying tissues of the uterus, with their abundant blood supply. This structure, made partly from the embryo, partly from the mother, is the placenta, chief organ of our embryonic life.

THE DEVELOPMENT OF FORM

Third week

We have run somewhat ahead of our story in taking up the final development of the embryonic membranes—now to go back and notice a few things that have been happening in the meantime.

When we are about two and a half weeks old, the floor of the cavity roofed by the amnion is still quite disk-shaped. It is from this disk that our body will form. But growth is proceeding rapidly only at one end of it, so that the disk soon becomes pointed and elongated. The primitive streak appears in this region of rapid growth, with the pore into the gut at its anterior end. The amnion meanwhile has separated from the chorion everywhere along the top except at the posterior end of the embryonic disk, so that the body stalk is here. In just a day or two our length doubles, while there is no increase in width (Fig. 74).

Next, the region in front of the pore begins to grow more rapidly than the hinder part, and the relative positions of the pore and the primitive streak are thus pushed farther and farther back. From the pore a shallow neural groove extends forward toward the head, and just under this groove a long rod of mesoderm grows forward from the front lip of the pore. At this time, too, we begin to get some thickness to our bodies. No longer so nearly like a plate spread on top of the yolk sack, the body stands out above it like a cylinder, slightly sway-backed in the middle.

The side walls of the body roll in underneath and cut off a tubular portion of the gut cavity from the yolk sack, leaving them communicating only in the center. At front and rear the tips of this digestive tube lengthen until they touch the body surface, leaving only a thin membrane. These will eventually rupture to open up *mouth* and *anus*.

The roundworm, which has been mentioned already in

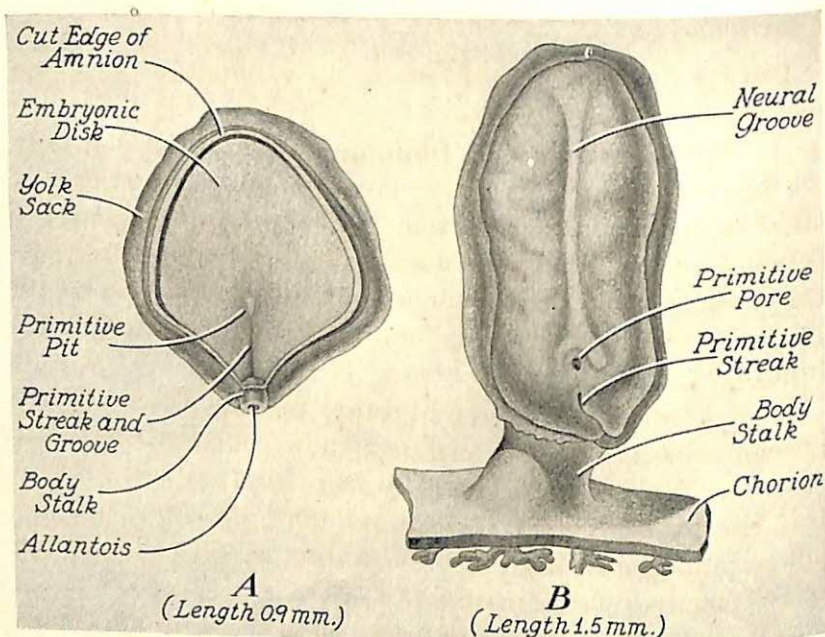


FIG. 74. Early human embryos seen from above. *A*, about seventeen days old (Streeter). *B*, about twenty days old (Spee). (Redrawn with modifications from Arey's *Developmental Anatomy*. Courtesy of W. B. Saunders Company)

connection with the body cavity (see p. 248), is a fair representative of an animal which stops on this general level of development. It has a digestive tube, running all through the body from mouth to anus, and a body cavity, with mesoderm lining one side (the outer). The nervous system, however, forms on the underside, and is not a hollow tube; nor is there any sign of a rodlike structure down the back. These last two are features found only in animals much closer to us in the scale. Yet we should not imagine that roundworms are altogether simple and primitive creatures. They are often specialized in amazingly individual ways for the life of a parasite, and they are the first examples we meet whose individuals are wholly male or female. Even the much more complex segmented worms are hermaphroditic.

Fourth week

During the fourth week of our lives important developments come thick and fast.

(1) The neural groove running forward from the pore deepens, folds grow up along it and arch over toward one another, finally fusing to make a tube, the rudiment of the spinal cord. In front the tube broadens out into three successive bulges, which take longer to close. These vesicles are the three original parts of the brain: forebrain, midbrain, and hindbrain.

(2) Underneath the neural tube, the rod of mesoderm growing forward from the pore is now complete. It is the forerunner of the backbone, and runs from the tail well up into the head. Tough, though not bony—for bone first develops a good deal later—this *notochord*, as it is called, is the first skeletal structure to appear.

(3) Mesoderm lying to the sides of the notochord begins to be divided into blocklike segments, arranged in pairs to right and left. These first show up just back of the hindbrain; and, as the neural tube progressively closes over in the direction of the tail, the paired segments keep pace with it. By the end of the week the entire thirty-eight pairs have appeared (Fig. 75).

(4) Blood vessels, blood, and a heart begin to develop from the mesoderm.

(5) In the head and neck region small tubes grow in the mesoderm, a pair to every pair of segments. At one end each tube opens into the body cavity; at the other, it turns toward the rear and grows until it meets the tube in the next segment, thus forming a duct which soon connects all the tubes on one side of the body (see Fig. 84, p. 283). These are excretory tubules. The two ducts grow back until they empty into the cloaca.

Earthworms and their marine relatives halt at a similar stage of the developmental journey. They are obviously seg-

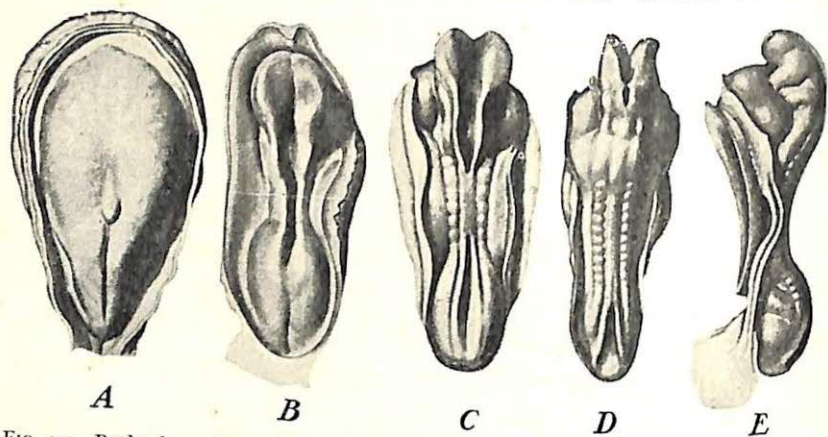


FIG. 75. Body form in early human embryos. *A*, the primitive streak stage, nineteen days old (magnified about 32 diameters). *B*, with 3 mesodermal segments and a deep neural groove, early in the fourth week (magnified about 30 diameters). *C*, with 7 segments; neural tube closing (magnified about 25 diameters). *D*, with 10 segments; brain vesicles closing (magnified about 25 diameters). *E*, with 19 segments, twenty-five days old, with a well-folded cylindrical body (magnified about 16 diameters). All but *E* are in dorsal (surface) views; *E* is seen from the side. (From Arey's *Developmental Anatomy*, after Streeter. Courtesy of W. B. Saunders Company)

mented, and they have a well-developed circulatory system, with blood, arteries, veins, and even pulsating vessels that do the work of a heart. They also have a pair of excretory tubules in each segment. These open into the body cavity at one end, like ours; at the other, however, while they pass to the rear, they open separately through the body wall instead of forming two continuous ducts, each opening to the outside at one point only.

Earthworms, however, like roundworms, have their nervous system running down the ventral (belly) side instead of down the dorsal (back), like ours; and they have no trace of a notochord. A notochord and a dorsal neural tube make their appearance only in the lowest members of the great phylum of the chordates, to which we belong. These primitive chordate relatives of ours are queer enough, to be sure, and one of them is distinctly like a worm in outward appearance.

If we continued to examine our embryonic development in this fashion, week by week, we would see again and again that various groups of animals which have been developing as we do halt or pursue side lanes of specialization. In the little lancelet (*Amphioxus*), which looks like a fish without jaws or paired fins, ears, or eyes, and has neither bones nor cartilages, there are not only a notochord and a dorsal neural tube but also several dozen *gill slits*, opening in pairs from the pharynx to the outside. This is a feature which we develop in our fourth week, although the pouches in our throat and the grooves which form in the skin above them are separated by a thin membrane which is usually never ruptured. Nor have we as many gill slits as the lancelet—only four furrows on each side are visible externally, and inside only five pairs of pouches can be counted (Fig. 76).

Later in this same week our eyes and internal ears appear, lateral projections on the head grow together to form jaws, two pairs of limb buds pop out, and, within the body, cartilage (gristle) begins to form from parts of the mesoderm. Here we part company with the sharks and rays. In our eighth week bone begins to form around the notochord in blocks—fishes share a backbone with us, but develop a swim-bladder and fins as we go on to develop lungs and limbs. The amphibians—frogs, toads, newts, and salamanders—are kept close to water because their eggs must develop in it. They are not provided with an amnion to protect them or an allantois for respiration and excretion before hatching from the egg. Only reptiles, birds, and other mammals accompany us here. Finally, only mammals form a placenta for the prolonged nourishment of the embryo within the mother's uterus, grow hair, and produce mammary glands for suckling the young.

Step by step we pass the stages where we become readily distinguishable from fish, from frogs, from reptiles and birds, from other mammals, and finally from the monkeys and

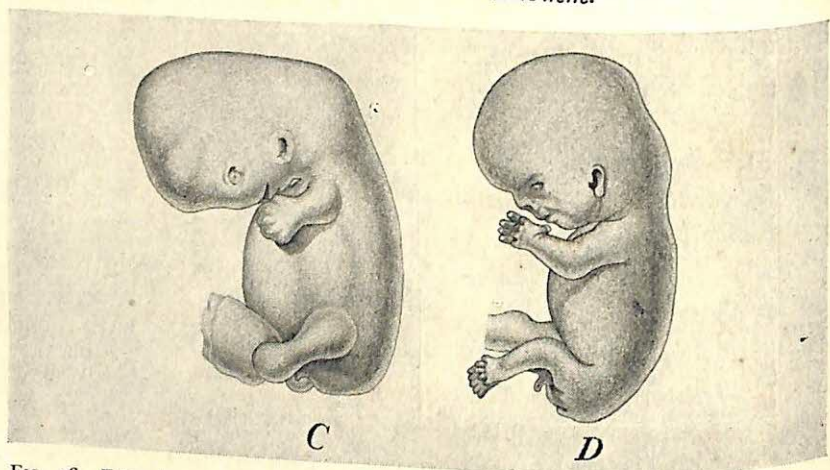
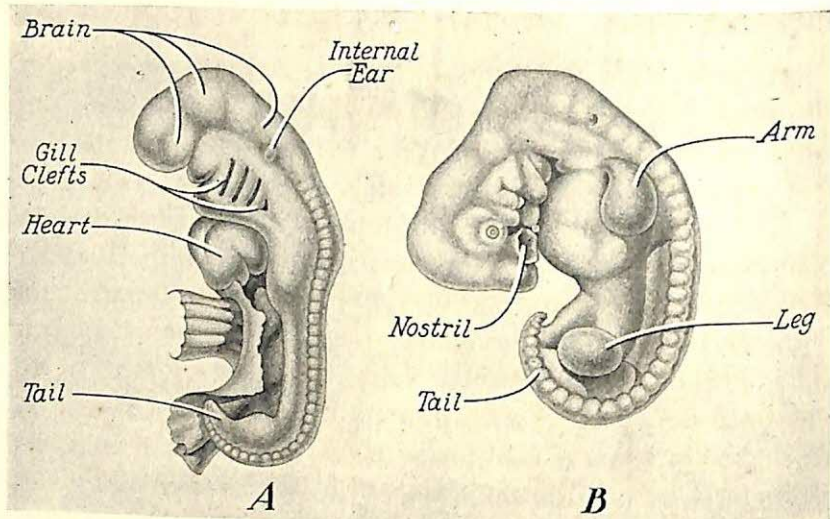


FIG. 76. Four stages in the development of form in the human embryo. *A*, about four weeks old (4.2 mm.). *B*, about five weeks old (7.5 mm.). *C*, about seven weeks old (18.1 mm.). *D*, about two months old (23 mm.). The bars indicate the actual crown-to-rump lengths of the embryos. (Redrawn: *A*, with modifications from Arey's *Developmental Anatomy*, after His. Courtesy of W. B. Saunders Co. *B*, with modifications from Marshall's *Vertebrate Embryology*, after His. Courtesy of G. P. Putnam's Sons. *C*, from Minot's *A Laboratory Text-Book of Embryology*, ed. 2. Courtesy of The Blakiston Co. *D*, from Bailey and Miller's *Text-Book of Embryology*, ed. 5, after His. Courtesy of William Wood & Co.)

apes. *When two months old, we are recognizably human*, although our proportions are anything but what they are later. The furrows in the neck have disappeared, and the tail, so prominent at six weeks, is about gone. Our head is still as large as the rest of our body, with very weak chin, flat nose, and eyes far apart. But it is definitely a face and not a monstrous caricature. There are tiny fingers and toes on the limbs, and before the end of another month sex can be readily distinguished. Muscles, too, begin to twitch and gain strength through exercise at this time.

From now on the outward changes are mostly in proportion, because of altering rates of growth in different parts of the body. There is, of course, an enormous increase in size and weight, for at the eighth week we weigh only one gram ($1/28$ oz.) and from crown to heels measure slightly more than an inch, while at birth we are on the average 3,300 times as heavy and seventeen times as long. Yet, as a matter of fact, *we actually grow more and more slowly*, for while we still have most of our weight to put on, it is steadily less in comparison with the total. During the first month of our growth we increase our weight about 40,000 times; during the last month before birth, we increase it by only a little over one third!

ADEQUATE DISTRIBUTION—A CIRCULATORY SYSTEM

Up to this point we have traced the major events in our development in a single sequence, but now the stage becomes overcrowded and it grows ever more difficult to keep all the threads of the plot in mind at once. It seems better to consider each great life problem separately, and to see how each in turn is met.

The first system in our bodies to reach a functional level is neither the digestive nor the nervous system, even though these, as we have seen, are started much before any others.

The reason for their tardiness lies in the special provision for nutrition, respiration, and excretion made for all mammalian embryos through the placenta. There is no significant need for a system to digest food that enters our bodies from our mother's blood already predigested. Nor is there need for a system to coordinate responses before any effective means of making responses has developed! There is, however, from very early in our growth a need for an effective carrier of dissolved foods, oxygen, and wastes. *The first system to begin functioning as a whole is the circulatory system.*

Shortly after the mesoderm splits and forms a body cavity, blotches begin to show up in the mesodermal layer next to the endoderm, out on the yolk sack. These are groups of cells known as *blood islands*, for some of them differentiate into red blood cells, and others become flat and line spaces in the mesoderm that gradually fuse into primitive blood vessels.

The blood

The blood itself is composed principally of water containing: (a) dissolved salts, in concentrations strikingly similar to those in sea water; (b) dissolved foodstuffs and wastes; (c) colloidal proteins, among them those responsible for the capacity of the blood to clot, and the resistances to various diseases, poisons, or the allergies to various foods or pollens; (d) the several types of white blood cells, helpful in combating bacterial invasions; and (e) the red blood cells, whose function is to convey oxygen to the body cells in union with hemoglobin. Hemoglobin contains iron, and its synthesis is the most important use of this element in the body. The blood cells are formed during development in a variety of places, first, as we have seen, in the blood islands of the yolk sack. A week later, they are produced in the unspecialized mesoderm of the body and in the blood vessels; the following week (the sixth) the factory shifts to the liver. Some weeks later the spleen, the thymus, and the lymph glands take over; and from the third month, with the development

of the long bones, the red bone marrow within them becomes the main source of the red blood cells, and after birth the only source of all types of blood cells. An interesting fact is that the first red blood cells are released into the blood stream while still large and nucleated, like those of fishes. These give place to a type with a smaller nucleus, like those of reptiles and birds, and only in the liver is there produced for the first time the mammalian type, which loses its nucleus before it enters the circulation and thereafter cannot undergo mitosis.

When and where the blood proteins are first produced is a matter of doubt. Later, the liver is their chief source; but some kinds come from the ameboid cells of the spleen, lymph tissues, red bone marrow, and the epithelium of sinuses and blood vessels. At all events, it is certain that, although the capacity to produce is present, actual production in many instances (immunities, allergies, and so forth) occurs only after exposure to the *antigen*, a foreign protein substance. The capacity of the blood to clot is also slow in developing. An infant's blood clots poorly until eight days after birth, and not with normal speed for about a year. This incapacity is sometimes fatal at birth, for the squeezing which the skull must undergo in passing through the pelvic ring of the mother often results in small brain hemorrhages, particularly in the prematurely born. An estimated one fourth of all birth injuries are due to this. For some time it has been known that vitamin K, found most abundantly in spinach and alfalfa, but scarce even there, is necessary for the production of normal amounts of prothrombin, one of the substances requisite for clotting. Feeding the vitamin to an expectant mother or to the newborn infant is effective in speeding up the development of prothrombin, and so in bringing about normal clotting. We have here an excellent example of the way in which a normal rate of development is conditioned by the abundance of a necessary raw material in the environment.

The blood vessels

In the fourth week, the primitive vessels have developed into a symmetrically paired system, looping down over the yolk sack, then up into the head, and along the back toward

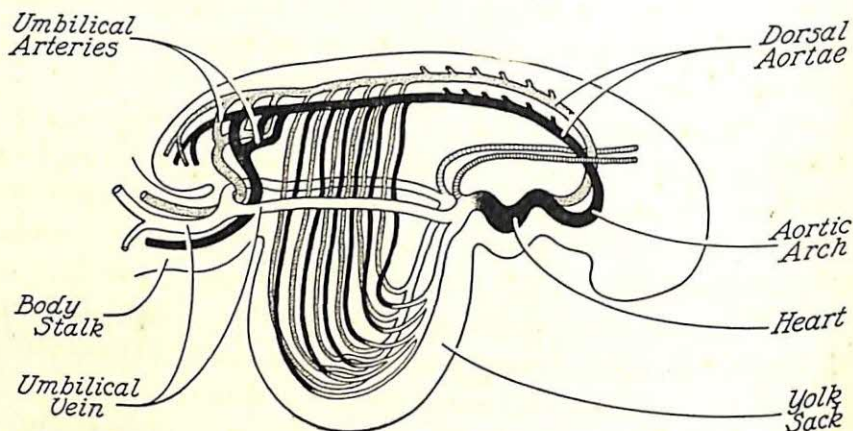


FIG. 77. The human circulatory system at about three and one-half weeks. Arteries are shown black or stippled; veins are shown in outline or cross-hatched. (Redrawn with modifications from Arey's *Developmental Anatomy*, after Felix. Courtesy of W. B. Saunders Company)

the tail, giving off the branches to the yolk sack and other developing organs. Two of these branches are exceptionally large and follow the allantois into the body stalk. They are the umbilical arteries. Only one large vein comes back from the umbilical cord, but it forks as it enters the body and passes toward the head. Also by this time the two big blood vessels in our necks fuse; and this rudiment of a heart begins to pulsate, at first feebly, then stronger and more rhythmically, pumping the fluid in the vessels forward to the head, then down the back and around to the heart again (Fig. 77).

Blood vessels carrying blood away from the heart are called *arteries*. Those bringing blood back to the heart are called *veins*. (In Fig. 77 arteries are solid black or stippled and veins are in outline or crosshatched.) In the placenta and in

all the organs blood is conveyed from arteries into veins through a network of myriads of microscopic blood vessels, the *capillaries*. These have such thin walls, no more than a single layer of very flat cells, that water and most dissolved substances can readily enter and leave the vessels. Thus the spaces between cells are filled with a fluid that is blood strained of its solids. From this fluid food and oxygen enter the cells by osmosis and wastes are received in return.

The circulatory system is at this time a single circuit. All blood leaving the heart through the arteries is distributed to the body or placenta, passes through capillaries, is collected into veins, and returns to the heart. With each circuit some of the blood—that which goes to the placenta—is purified of wastes, and receives a fresh supply of food and oxygen. Part of this blood, after returning to the heart, is sent to the body, but part of it is returned to the placenta. And each time, too, some of the blood, filled with wastes, and needing replenishment of foods and oxygen, is, nevertheless, distributed again to the organs. This is certainly not very efficient, but still we manage to get along.

The remainder of the development of our circulatory system is largely concerned with remodeling this one-circuit system into an efficient double circuit. All the blood from the body is pumped to the lungs for a fresh supply of oxygen, and all the blood from the lungs is pumped to the body. In this change the lungs take the place of the placenta in the system.

In some respects the single-circuit system is more complex than that which takes its place. An early simplification is a fusion of the two big arteries along the back into a single one, the *aorta*, or trunk artery of the body. In front, however, the double system persists. Through the fourth, fifth, sixth, and seventh weeks these paired loops, or arches, of the aorta go through an extraordinary transformation. They keep forming short cuts until there are five main pairs of

arches, and even traces of a sixth. Meanwhile those in front, like oxbows in a river which have been robbed of their water by by-passes, dwindle away, either wholly or in part.

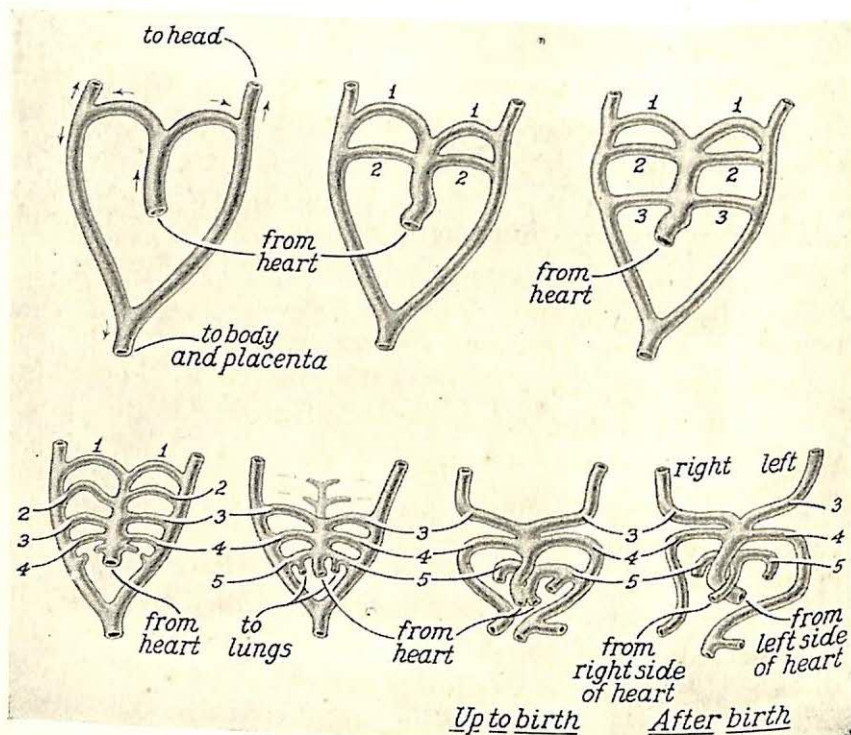


FIG. 78. Diagrams illustrating the successive changes in the human arterial arches up to and after birth.

As seen from below (a ventral view), the system alters successively as shown in Fig. 78.

The first two pairs of aortic arches (1, 2) degenerate entirely.

The dorsal connections between the third and fourth pairs of aortic arches (3, 4) degenerate, and thereafter the third pair supplies blood only to the head.

The right arch of the fourth pair breaks away and supplies blood only to the right shoulder and arm.

The left arch of the fourth pair becomes the trunk artery, the *dorsal aorta*.

The final or pulmonary pair disjoins so as to supply only the lungs.

A spiral partition grows up the aorta, so that the pulmonary arches get blood from the right side of the heart, and the other arches from the left side.

This extensive revision may appear quite incomprehensible to us. Yet there is a reason why it occurs in this fashion. We may notice, for example, that the digestive tube produces a pouch between each of these pairs of arterial arches, and that a corresponding pocket forms in the outer skin. These keep deepening until they nearly meet—only rarely do they break through to become perforations of the throat. And we may notice that in the mesoderm alternating with these pouches and pockets supporting bars of cartilage develop. Now suppose we look at a fish. We see at once that what we have been looking at is the exact arrangement of a fish's gills. Except that in a fish the pouches and pockets open all the way through, so that water swallowed through the mouth can exit through these holes in the neck, and except that the arteries branch into an intricate capillary system in the arches, and thus are able to exchange oxygen and carbon dioxide more effectively with the water, the arrangement is identical.

The conclusion is unavoidable. *Our whole neck region, including these arterial arches just described, develops first in a fashion appropriate for a gill-breathing fish, and then is re-adapted by extensive remodeling for breathing in the air.*

The heart

The heart, too, has been revised in the meantime. From a simple pulsating blood vessel, it is first improved by a development into two chambers. The first, receiving blood from the veins, is rather thin-walled; the second, at first nearest the

head, pumps the blood out through the arches, and its walls grow much thicker and more powerful. A valve which prevents any back-flow of the blood is formed where the trunk vein enters the heart, and another at the exit into the aorta. As the heart lengthens faster than the body, it becomes coiled into a complete loop, so that the *ventricle*, the thick-walled chamber, no longer lies nearest the head (Fig. 79).

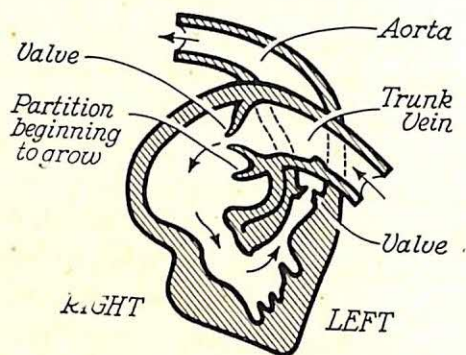


FIG. 79. Diagram of the human heart at the end of the fourth week of development, when it is in a simple two-chambered condition, in the shape of a loop consisting of a chamber (*atrium*) into which the trunk vein (*sinus venosus*) empties through a valve, and a second chamber (*ventricle*) opening into the aorta.

This two-chambered heart is as far as fishes ever get, except the lungfishes, and for the requirements of a fish it is ideal. All the blood from the body is pumped to the gills for a fresh load of oxygen and a removal of carbon dioxide, before it passes to the organs of the body.

How can such a pumping organ be transformed into one just as efficient for a double circuit? That is the problem of our circulatory development. Blood from the body must, after birth, be pumped to the lungs; and blood from the lungs must be kept separate and pumped out to the rest of the body. This involves a division of the heart into essentially two hearts, side by side. A partition grows down through the heart—its beginning may be seen in Fig. 79—to the left of the opening of the trunk vein. Another partition

grows up from the bottom of the ventricle and connects with the spiral partition which has separated the aorta from the arteries to the lungs. Valves then develop between the two chambers on each side of the heart. In this way blood from the left ventricle is pumped into the aorta and that from the right ventricle goes into the pulmonary (lung) arches.

In the lungfishes and *Amphibia* (frogs and toads, newts and salamanders), animals which have become only partially adapted to air-breathing, the first of these partitions forms, but the second does not. This is also true of most reptiles. Except for the *Crocodylia*, which have both partitions, although imperfect and perforated, only birds and mammals have four-chambered hearts.

Before birth, however, our lungs are not functioning. Some blood goes to them, but much of what flows through the pulmonary arches passes through the still persisting connection to the aorta. The left side of the heart would therefore receive less blood, and the aorta would also be rather empty, were it not that the partition between the two upper chambers of the heart remains incomplete, so that blood from the right side passes over to the left. As a matter of fact, there are actually two incomplete partitions, growing from opposite sides, with their openings slightly overlapping (see Fig. 80). Most of this blood passing through the openings in the partitions has come directly from the placenta and is well oxygenated. It is thus shunted directly to the head and body without having to pass first through the lungs.

At birth, as the lungs are inflated, the connection of the pulmonary arch on the left side to the dorsal aorta is shut off (see Fig. 78) and all the blood from the right side of the heart is shunted to the lungs. The blood returning from the lungs to the left side of the heart thereafter keeps the left auricle filled. The pressure against the two partitions holds them together until they grow into one. The gap closes and the two sides of the heart are thus completely separated. Whenever this gap remains incompletely closed, the double circuit of

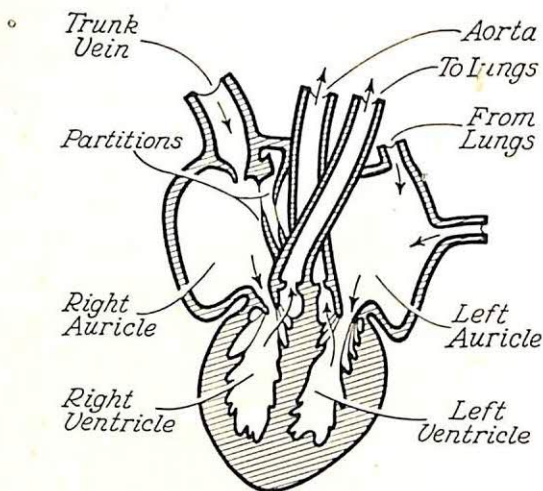


FIG. 80. Diagram of the human heart in a six- to eight-weeks-old embryo. It is in a four-chambered condition. There is a double partition between the two auricles, each partition with an oval aperture in it. The state as pictured persists until birth, with the exception that the trunk vein is taken into the right auricle and its valve disappears and that the two pulmonary veins emptying into the left auricle are absorbed by its growth past the points at which they each fork, so that four, instead of two, pulmonary veins enter the mature left auricle. After birth the two partitions between the auricles coalesce, and the passage of blood between the latter is blocked. The circuit of the blood through the heart, indicated by the arrows, remains essentially unchanged.

the blood through the heart is imperfect. This happens in about one baby out of four, but only rarely is it so serious that enough blue blood leaks through from the right side to the left to tinge with blue all the blood going to the body. These rare "blue babies," or "mourning babies," as they are commonly called, usually die from lack of sufficient oxygen in the blood going to the body.

ADEQUATE NUTRITION—A DIGESTIVE SYSTEM

We have already seen that after four weeks of development the digestive tube reaches from mouth to anus, with two bladder-like outgrowths, the yolk sack and allantois. Shortly after

this a number of buds appear at various places along it, giving rise to a number of pouches (Fig. 81). One of these buds, just in front of the yolk sack, enlarges to form the liver. It

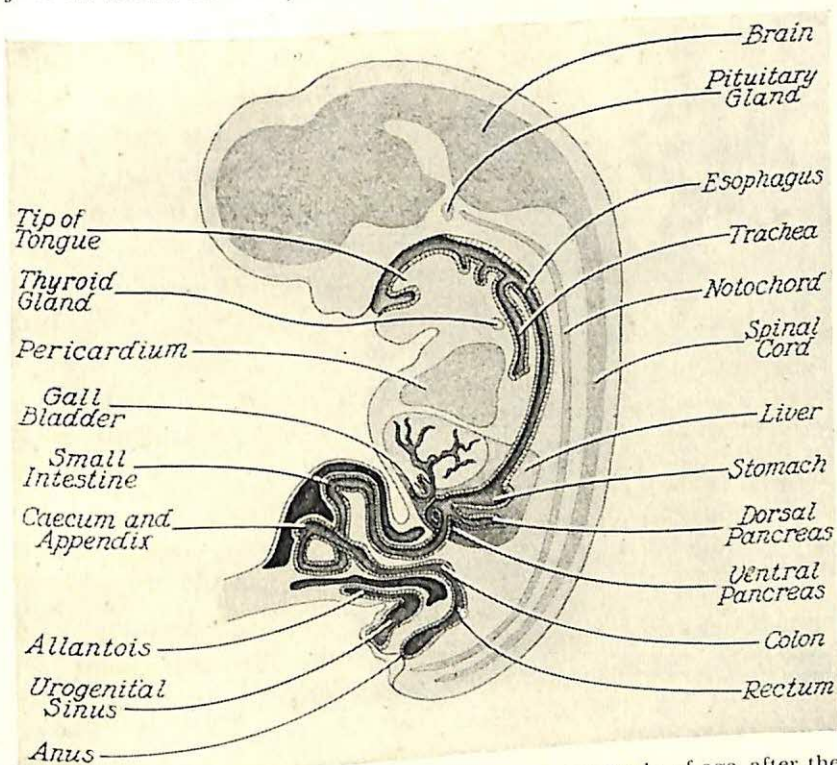


FIG. 81. Right half of a human embryo at about seven weeks of age, after the intestine has pushed a loop down into the umbilical cord and the cloaca has become divided into rectum and urogenital sinus. The pericardium is a sack-like membrane surrounding the heart. Magnification about $4\frac{1}{2}$ diameters. (Redrawn with modifications from Arey's *Developmental Anatomy*, after Mall. Courtesy of W. B. Saunders Company)

grows enormously and at nine weeks is by far the largest organ in the body. It grows about the umbilical vein, which then forms a meshwork of large thin-walled vessels within the liver. In this way the blood from the placenta, with its fresh load of food, is brought first to the organ which later assumes the function of changing sugar into glycogen for temporary

storage. The veins from the intestine are also collected into a big vessel which runs through a similar meshwork of vessels in the liver. Thus at birth all is ready for the digestive system to supplant the placenta without upsetting the means developed for providing a temporary storage of carbohydrate in the liver.

The blood from the placenta or, after birth, from the small intestine brings to the liver a supply of amino acids. Such of these as are required for the synthesis of proteins are carried through the liver and distributed to the body cells. But amino acids are also used to supply energy through oxidation. Before the latter use can be made of them, the amino groups must be removed from the amino acid molecules. This is done in the liver, and ammonia is produced. The ammonia is then used in neutralizing various acids that are formed in metabolism. A large portion of the ammonia unites with carbon dioxide to form urea. This waste product is carried by the circulation back to the placenta or, later on, to the kidneys, whence it is excreted.

These are not the sole functions of the liver. Another vital one is its role as an excretory organ. The red blood corpuscles can function efficiently only for two or three weeks—then they “wear out” and must be replaced. The task of the removal of the aged ones falls to certain cells in the liver. These, like the white blood cells, live and move freely about in the blood vessels. Unlike the white blood cells, they stay within the limits of the liver, and, instead of ingesting bacteria, they prey upon ageing and worn-out red blood cells. These are broken down, and, while the iron of the hemoglobin is largely saved for re-use, other parts of the pigment are converted into bile pigments, greenish in color. From three months on, bile is being secreted. From the neck of the duct connecting intestine to liver there also grows a side pouch. This is the *gall bladder*, which stores the bile temporarily. After birth, whenever food enters the intestine from the stomach, bile will be released and mixed with it. Organic salts in

the bile help to break up fats into smaller droplets, thus aiding the action of the digestive enzymes.

Two other small pouches bud from the digestive tube close to the outgrowth that makes the liver and gall bladder. One is very close to the liver bud; the other is on the back side. These bend around until the glands that grow from them fuse into a single flat, lumpy *pancreas*. This gland has secreting cells which are ready to produce some of the principal enzymes used in digestion after birth.

Other parts of the pancreas are of more immediate importance. These are groups of gland cells, the *islets of Langerhans*, which secrete their product into the blood rather than into the ducts leading to the intestine. This substance is *insulin*, and it regulates the concentration of sugar in the blood, both by controlling its use in the cells and by its storage, through conversion into glycogen, in the liver.

Meanwhile the intestine itself has done some extensive growing. At four weeks it curls directly around into the tail, but by five weeks it has lengthened so much faster than the body that it forms a big loop, while the extension into the tail has disappeared. About halfway from the liver bud to the anus, a little pouch (the *caecum*) appears which marks the place where the small intestine will enter the large intestine. The tip of this little pouch becomes the *appendix*. The yolk sack is pinched off from the gut, and a partition separates the allantois and urinary bladder from the gut, as has already been described. At ten weeks the anal membrane ruptures, and the digestive system finally becomes a tube, the mouth having been opened considerably earlier. The layer of mesoderm around the digestive tube forms a double muscle layer, with fibers running circularly and lengthwise. With rhythmic wavelike contractions called *peristalsis*, these will push the contents of the intestine along as the food is digested and absorbed. Glands, too, are formed in the endodermal lining of the intestine. Some of these, mainly in the large intestine, secrete a slimy *mucus* which lubricates the intestine. (Water

is principally absorbed from the large intestine; and as the contents become more and more solid, additional lubrication is required.) In the small intestine the glands secrete intestinal digestive juice, containing enzymes complementary and supplementary to those of the pancreas.

The lining of the small intestine becomes covered with millions of small projections that make it look like velvet. These are the *villi*, which will absorb the digested foodstuffs. They greatly increase the absorbing surface of the intestine. Each villus has a central vessel filled with *lymph*, a fluid essentially like blood plasma. All these lymph ducts are gathered into a great central duct which traverses abdomen and chest to enter the large vein from the left shoulder, providing for future use a direct route to the center of distribution for the absorbed fatty acids and glycerin, quickly recombined into fats. Each villus also contains a capillary network which enables the sugars and amino acids, absorbed directly into the blood, to go immediately to the liver (see pp. 269-270).

Above the buds of liver and pancreas a swelling in the digestive tube makes its appearance. This enlarges to form the *stomach*. Its inner lining becomes wrinkled and folded even more than that of the intestine and comes to contain thousands of gastric glands, able to secrete hydrochloric acid and the digestive enzyme *pepsin*, which begins the work of protein digestion. The stomach muscles wax extremely thick, and indicate what will be the chief action of the stomach on food, that of churning it and breaking it up mechanically into small particles which the digestive juices in the intestine can readily attack. Around the junction of stomach and small intestine an exceedingly strong ring (*sphincter*) of muscles develops, controlling the exit of food from the stomach and generally letting it through only in small amounts, after it is sufficiently broken up. This food is, of course, acid in reaction. Gland cells sensitive to acid develop in the upper part of the small intestine, where, when stimulated, they will secrete a substance into the blood. This substance, *secretin*,

when carried to the pancreas and liver, starts the flow of pancreatic juice and bile from those organs. All of this digestive apparatus is ready for work before birth, although, to be sure, it can handle only milk at first, and must gradually become accustomed to other foods. This is true for all mammals, but, as we have no doubt observed, the young of birds or lower vertebrates can handle adult foods immediately after hatching.

The pharynx and its outgrowths

The part of the digestive tube just back of the mouth is the *pharynx*. It produces a number of important pouches (Fig. 82). Hindmost of these is a ventral pouch which elongates in measure with the narrow *esophagus*, that part of the digestive tube connecting pharynx and stomach. During the fourth week this lengthening pouch forks, and the two buds on the ends rapidly enlarge into lungs. These will be discussed more fully in connection with respiration.

In front of this, five pairs of pouches bud out on the sides of the pharynx, the largest pair nearest the mouth. These are the gill pouches we have spoken of in connection with the aortic arches. Between the first pair of pouches another ventral pouch buds off to make the *thyroid* gland, which soon loses its connection with the pharynx.

We have, of course, no use for gill pouches as such. During the second month of our development, they either are modified into useful structures or degenerate entirely. The first pair of pouches, nearest the mouth, alone remains recognizable. These grow in length, keeping up with the thickening of the head, until they form on each side a slender tube ending in a larger cavity just over the primitive ear. The corresponding external pockets, or grooves, also deepen to form the ear pits. The region separating the ear pit and the inner pouch becomes modified into an eardrum of three layers, two of epithelium with a fibrous layer sandwiched in between them. After birth the *Eustachian tubes* from the pharynx to the ear cavity beneath the drum will be very useful in equal-

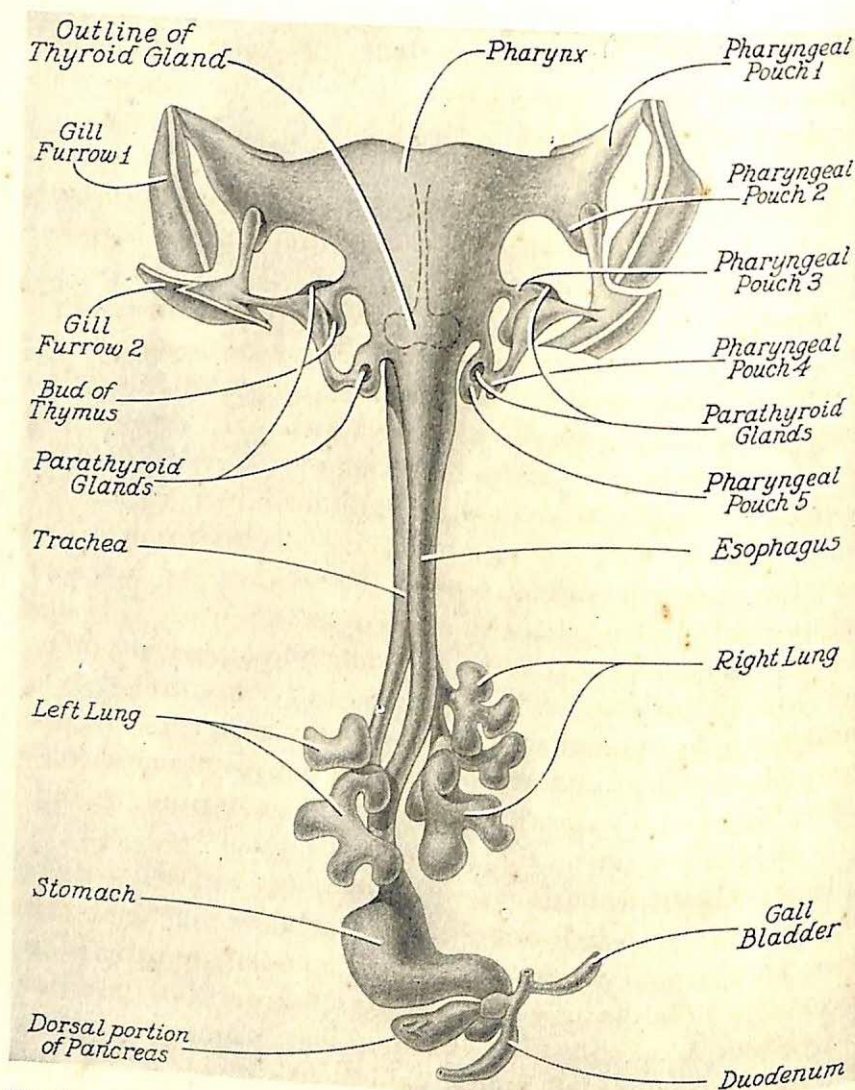


FIG. 82. Reconstruction of the upper digestive tract of a six-weeks-old (12 mm.) human embryo, seen in dorsal view, so as to show the outgrowths of the pharynx. The thyroid gland, located on the ventral side, is indicated only by its outline. (Redrawn with modifications from Arey's *Developmental Anatomy*, after Hammar. Courtesy of W. B. Saunders Company)

izing the air pressure on the two sides of the eardrum, but they are also a source of considerable trouble, since they provide an entrance for germs into the ear. Especially in babies, when these tubes are relatively short, this is the source of many earaches.

From the tips of the second pair of pouches grow the two *tonsils* located on the sides of the pharynx. They are lymph glands, of which there are great numbers in the body, and so individually are not of vital importance.

From the fore tips of the third and fourth pairs of pouches develop four little pea-sized glands. In the adult these come to lie just behind, or buried within, the thyroid. They are the *parathyroid glands*, of vital importance in controlling the concentration of calcium in the blood.

From the hind tips of the third and fourth pairs of pouches there grow glands which fuse to make the large *thymus*. The function of this organ is somewhat of a mystery, as it is largest before birth and steadily decreases in size thereafter. (Sometimes in babies it is so large it hinders breathing and must be reduced by x-ray treatment to avoid suffocation.) It is thought to regulate growth and development during the embryonic period and infancy, for later its removal is not serious.

Nothing of importance is known to develop from the fifth pair of pouches.

In all but the first pair, the corresponding external grooves or pits fill in and disappear. Only rarely does the membrane between external groove and internal pouch rupture, so as to make a hole entirely through the neck into the pharynx. Sometimes a cyst in the neck is formed from incomplete obliteration of one of the external clefts.

The *tongue* forms as an extension of the muscular floor of the pharynx, and grows forward into the mouth.

The mouth

In the fourth week of life the digestive tube breaks through the body surface to form a mouth. It is at first just a hole.

There are no jaws. Three pairs of pouches grow from its walls to make the three pairs of *salivary glands*. These will secrete a watery fluid of value in lubricating the food for swallowing and also containing an enzyme, *ptyalin*, which acts on starches.

Teeth begin to form at two and one-half months. Gland cells from the lining of the mouth begin to secrete the hard,

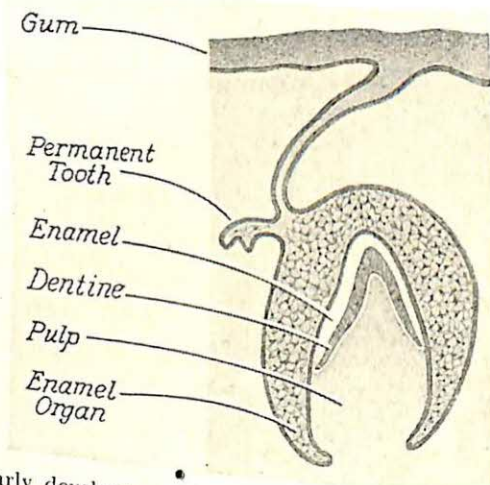


FIG. 83. The early development of a tooth—an incisor at the seventh (pre-natal) month. Magnified about 38 diameters. (Redrawn with modifications from Arey's *Developmental Anatomy*, after Tourneux. Courtesy of W. B. Saunders Company)

white enamel, and other cells from the mesoderm secrete the inner, softer dentine and the cement (Fig. 83). The jaw grows up on either side of the developing teeth until they are enclosed in a trench. Then bony ridges form between them, until each tooth is in its individual socket. When at length the crown of the tooth is complete, the enamel-forming organ degenerates, but the pulp which has been forming dentine remains in the tooth, a mixture of blood and lymph vessels and nerve fibers in a web of connective tissue. This is the live part of the tooth, commonly called its *nerve*. The time at which the milk teeth are cut varies with climate and nutrition and also genetically. But they usually follow a fairly

definite sequence, the middle incisors appearing first, in the sixth to eighth month after birth, and then the lateral incisors, the first molars, and the canines. Last come the second molars, often not until the third year. Reptiles have numerous sets of teeth which replace one another as their earlier sets are worn out, but we ourselves are limited to one replacement. The beginnings of the permanent teeth develop underneath the milk teeth and are already present one to three months before birth. The two extra molars of each jaw are developing even earlier, but the wisdom teeth are delayed until we are five years old.

From the back of the future mouth a small pouch grows up against the brain and is shut off. A pouch grows down from the brain just behind it, and the two together make up the important *pituitary gland*, whose control over growth, female sexual cycles, and other vital phenomena is of great importance and will require a whole discussion for itself.

A partition grows across the mouth from the sides, separating an upper nasal cavity from the mouth proper. This partition is the *palate*. The nasal cavity connects with two pits in the face to make the nostrils. The palate does not extend all the way back, so nasal cavity and mouth still connect at the beginning of the pharynx.

ADEQUATE PROVISION FOR BREATHING AIR—THE RESPIRATORY SYSTEM

Just as in the case of the digestive system, where we saw equipment for handling food provided long before the time when food first has to be handled—so here. A system for breathing air, for providing an adequate supply of oxygen to the blood, develops long before the moment when air first inflates the lungs, just after birth.

Already the body has developed the rudiments of a more primitive type of respiratory system, only to junk it. The aortic arches, the paired pouches along the pharynx, the cor-

responding external clefts, and the supporting bars of cartilage in the neck (of which more will be said in connection with the skeleton)—all these resemble parts of a gill system, like that of a fish, suitable for exchanging oxygen and carbon dioxide between blood and surrounding water. All the land-living, air-breathing animals develop a primitive gill system of this sort, and of them all only the amphibians ever use it for respiratory purposes during any stage of their lives.

In following the development of the digestive system, we learned of the origin of windpipe and lungs from a ventral bud on the pharynx. Fishes, while they lack lungs, develop such a structure too, though rarely forked. In only a few of them, however, is it of any help in breathing; and in most it serves as an air bladder which, when filled, makes the fish more buoyant, and when empty, heavier; and so helps the fish to rise or sink in the water with very little muscular exertion. Its use as a lung depends mainly on an abundant blood supply, on a tremendous exposure of blood to air in multitudes of capillaries spreading over a great surface. Only a few fishes, the lungfishes, are thus equipped. These are fresh-water fish, living in lands of frequent drought; and their ability to breathe air directly may frequently save their lives.⁶

The development of our own lungs follows the lines just indicated. The windpipe, or *trachea*, forks into two bronchi, and these in turn branch into numerous bronchial tubes. These branch again and again to form the multitudes of pouches in the lungs. The pulmonary pair of aortic arches sends arteries to these, arteries which branch into capillaries whose thin walls make up most of the surface of the air sacks. Thus, once all the blood from the right side of the heart is directed into the lungs—this, you remember, happens for the first time at birth—all the blood making the circuit is exposed to the air in the lungs. In about twenty seconds the blood

⁶ H. W. Smith has written entertainingly of the lungfishes and their place in philosophy in *Kamongo* (Viking Press, New York, 1932).

coursing through the lungs makes the journey from the right side of the heart back to the left. In the remainder of each minute it makes the circuit of the body and is back at the heart again, ready for another trip to the lungs. During the twenty seconds in the lungs the blood must lose most of its content of carbon dioxide and pick up a fresh load of oxygen.

Rapid work—it could be done only if the blood were exposed to a maximum extent. That means a lot of surface! *The structure of the lungs is simply a means of exposing to the air as great a surface as possible, while keeping the organs reasonably compact and away from the danger of evaporation.*

The gas exchange takes place by diffusion. Oxygen will pass into the blood because it is less concentrated there; and carbon dioxide will pass from the blood into the air, following its concentration gradient. Remember, however, that for substances to diffuse through a differentially permeable membrane, they must be dissolved. If the membrane, therefore, were not moist, diffusion would stop. This is sufficient reason for the internal situation of the lungs. Were they as exposed to the air as are the gills of a fish when it is taken out of the water, they too would speedily dry up and the gas exchange would stop. This is why a fish suffocates in air.

Because of the long passages through which the air must pass before it reaches the lungs, twisting ways through the moist nose, trachea, and bronchi, the air is thoroughly humidified before it reaches the air sacks, and has little drying effect. Nor is this the sole type of air conditioning provided. Certain cells lining the nose and trachea secrete slick mucus, which entraps dust particles and bacteria, while other cells, equipped with cilia, beat this phlegm up into the throat and nose where it can be eliminated.

Just back of the tongue grows a little flap called the *epiglottis*. Every time we swallow, the larynx moves up under the base of the tongue, and the back of the tongue pushes the epiglottis down over the opening to the trachea, providing an automatic guard against getting food into the lungs. This

is also prevented by a potent set of nervous reflexes, which, whenever a crumb gets past the epiglottis, starts a vigorous coughing. The danger is not primarily one of suffocation, but of infection. The lungs, warm and moist, are ideal abodes (from the germ's point of view). Food nearly always carries hordes of bacteria, and it becomes a matter of great importance to prevent their access to the delicate lungs.

The danger of suffocation is prevented in another way. Incomplete rings of cartilage develop one above the other, in the walls of the trachea and bronchi. These act as springs and serve to keep the passages always open.

Voice production

The upper part of the bud that produces the trachea and lungs becomes enlarged into a voice-box, the *larynx*. A pair of folds grows from its sides. These are the *vocal cords*. They can be stretched through the pull of muscles on cartilages in the walls of the larynx. When they are taut, air passing up from the lungs causes them to vibrate and produce a sound. Like strings, the tighter they are stretched, the higher pitched the sound.

During adolescence the vocal cords lengthen and thicken, and the whole larynx enlarges, especially in males. This is responsible for the change in voice at this period; for the longer and thicker a vibrating string, the deeper its tone.

Sounds from the larynx are shaped by the regulation of the mouth and throat into one or another of the vowels, and the tongue, teeth, and lips provide the various stops we call *consonants*. The resonance (tone quality) of a voice depends on the vibration of the sound in the nose, in the sinuses (hollow spaces) of cheekbones and forehead, in the throat and chest. All these are under voluntary control, which means years of effort and practice before we can reach the peak of skill in speech and singing. In the long road of growth and development birth is but a bend, not a beginning or an end.

Breathing

The first time our vocal mechanism is used is when we are ushered from the warm, dark shelter of our mother's body into the harsh brightness and cold of a new world. The reflex reaction to gasp and cry at this moment provides the usual impulse that starts the breathing mechanism functioning.

The lungs themselves are not muscular. How is the air in them, then, constantly replenished from outside? A frog simply closes its nostrils and swallows a gulp of air, but this method would not be effective for our greater needs.

The degree of inflation or deflation of the lungs depends on the equilibrium between their internal and external pressure. Their internal pressure is virtually that of the atmosphere, over which we have no bodily control. Their external pressure, however, is that of the chest cavity in which they lie, and since this is sealed we can control it. By upward and downward movements of the *diaphragm*, a dome-shaped muscle separating chest from abdomen, the pressure in the chest cavity is varied. When chest pressure increases above atmospheric pressure, air is expelled from the lungs and they deflate. When it falls below atmospheric pressure, air flows into the lungs and they are inflated. This muscular diaphragm is a unique characteristic of mammals. It develops from various parts of the thin layer of mesoderm that lines the body cavity and forms slings supporting the internal organs. In all vertebrates there is a transverse partition separating a space surrounding the heart from the remainder of the body cavity. In both birds and mammals an additional fold grows in from the sides and back of the coelom and separates off the chest and cavity; but only in mammals do muscles grow into this membrane, chiefly by migration from the neck, and convert it into an effective part of the breathing mechanism. Here again our own develop-

ment resembles that of a reptile, only to go considerably further.

Since muscles work only when they contract, and the contraction of the diaphragm increases the volume of the chest cavity, the diaphragm produces only inspiration directly. Expiration occurs when the abdominal muscles contract and push the internal organs up against the diaphragm. In its task the diaphragm is assisted by the rib muscles. The ribs slant from the backbone down toward their attachments to the breastbone. When the muscles between them contract, the ribs are pulled up in front. This deepens the chest and increases its capacity. The air pressure inside falls, and the lungs correspondingly expand.

Some babies cry a lot, but we should recognize that this may have its advantages. After a system commences to function, its further development and growth are very largely conditioned by the use it gets, and this is especially true of systems under voluntary control. Hence the value of exercise and practice. As the baby is growing rapidly, its breathing needs are constantly greater, and vigorous exercise of the breathing mechanism may help it to supply the demand by furthering its own growth.

ADEQUATE PROVISION FOR ELIMINATING WASTES—THE EXCRETORY SYSTEM

If the development of the circulatory and respiratory systems has seemed strangely roundabout, what impression will that of the excretory system make? For here the remodeling that goes on is even more extensive. Only with the third attempt are the final kidneys produced.

The excretory system starts to form in the neck region, in the seventh to the fourteenth mesodermal segments shortly after these are blocked out. Branches from the trunk arteries here pass in pairs to the walls of the body cavity, and each makes a little ball of capillaries situated in a hump projecting

out into the cavity. The wastes of metabolism, except carbon dioxide, which is eliminated through the lungs after birth, are thus brought by the blood to these humps, and there filter into the body cavity. Tubules (tiny tubes) grow in each segment from the body cavity into the mesoderm, and each then turns rearward to connect with the tubule in the next segment (see Fig. 84). Thus a duct is formed through which fluid wastes might pass all the way to the rear and empty into the cloaca.

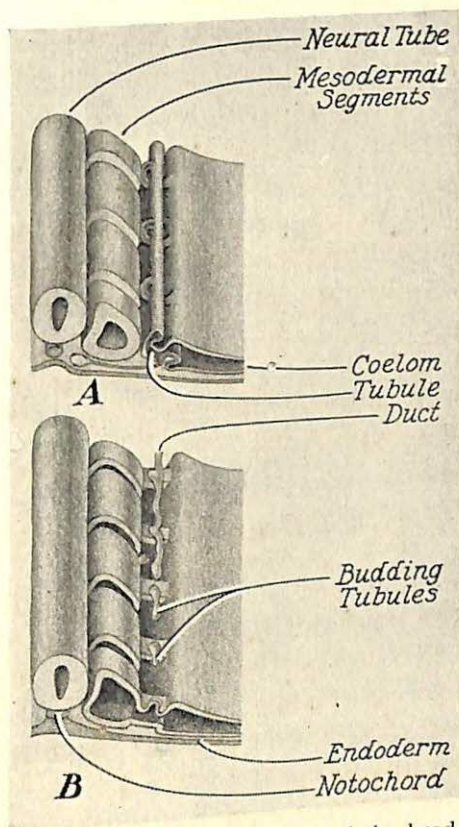


FIG. 84. Development of the tubules and duct of the head-kidney. *A*, anterior level of the embryo, with tubules and duct completed. *B*, posterior level, where tubules are still budding and linking together. (Redrawn with modifications from Arey's *Developmental Anatomy*, after Felix and Burlend. Courtesy of W. B. Saunders Company)

Since this most primitive excretory system begins to develop so far forward in the body, it is called the *head-kidney*. Segmented worms and *Amphioxus*, the lancelet, never get past a somewhat similar stage in the development of excretory organs. But this type of system has some pronounced disadvantages: The coelom is ineffective in collecting wastes

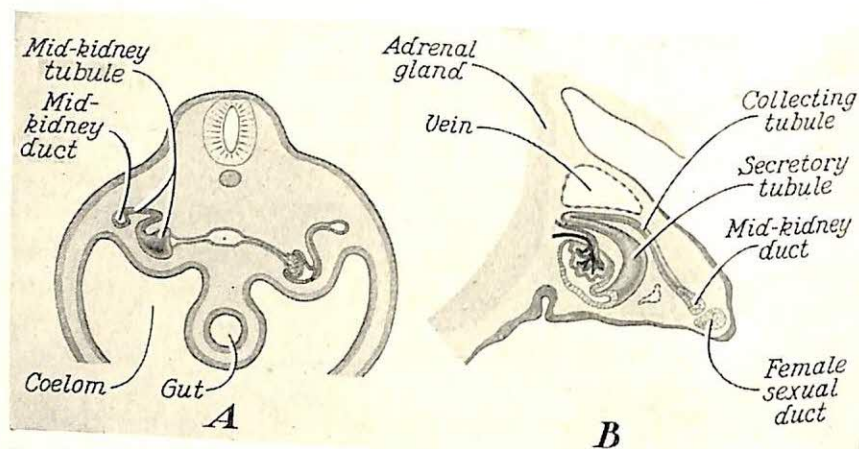


FIG. 85. *A*, cross section of a four-weeks-old (5 mm.) human embryo in the region of the mid-kidney, showing the form and relations of a mid-kidney tubule. *B*, cross section of the left urogenital ridge in a five-and-a-half-weeks-old (10 mm.) embryo, to show the character of a completed mid-kidney tubule and the relations of the mid-kidney duct and the female sexual duct. (Redrawn with modifications from Arey's *Developmental Anatomy*. Courtesy of W. B. Saunders Company)

from those cells that do not line it, and the transfer of wastes from the balls of capillaries to the mouths of the tubules is indirect. A second consideration is that the number of excretory tubules, if limited to one pair per body segment, might be altogether too few for a bulky animal.

Our next step in developing an excretory system obviates one of these disadvantages (Fig. 85). The mesoderm around the upper (dorsal) surface of the body cavity grows down like a cup to enclose each ball of capillaries. The wastes are then taken directly from the blood into the excretory tubules, and the body cavity loses all excretory function. Thence-

forward it is nothing but a space where organs may grow and expand.

The cells of the part of each tubule next to the capsule (the ball of capillaries and the cup around it) become tall and columnar, typical secretory cells. They extract the useful substances from the urine and return them to the blood, and also add to the urine certain protein wastes, unremoved by simple filtration.

This change in the type of excretory tubule takes place, however, only in the segments from the fifteenth on. The seven pairs of tubules in front of this, making up the head-kidney, degenerate completely before becoming functional. There are some eighty pairs of the new sort making up the second or *mid-kidney*. At any one time, however, not more than thirty to thirty-five pairs are present, for those in front begin to degenerate even before those in the rear segments have formed.

Although far more effective than the head-kidney, the mid-kidney, too, is inadequate for our needs. It serves well enough in fishes and amphibians, but in land animals it too is junked, like the head-kidney, although a part, here and there, is salvaged and turned to some new use. The majority of the tubules in each mid-kidney degenerate, but in males the two ducts remain and are utilized by the reproductive organs. In males, too, a number of tubules in the neighborhood of the testes are salvaged and used for storing sperms.

In the fifth week, each *hind-kidney* begins to form as a bud from the duct of the mid-kidney on each side (Fig. 86). Each bud appears just above the point where the mid-kidney duct it grows from enters the bladder. Each bud lengthens into a tube, or *ureter*, with a flared end, the *pelvis*, or collecting portion, of each kidney. From the pelvis of each kidney grow numbers of branches and into these empty tiers of excretory tubules, each similar to a mid-kidney tubule. There are about a million of these to each hind-kidney!

The gain in effectiveness through the development of the

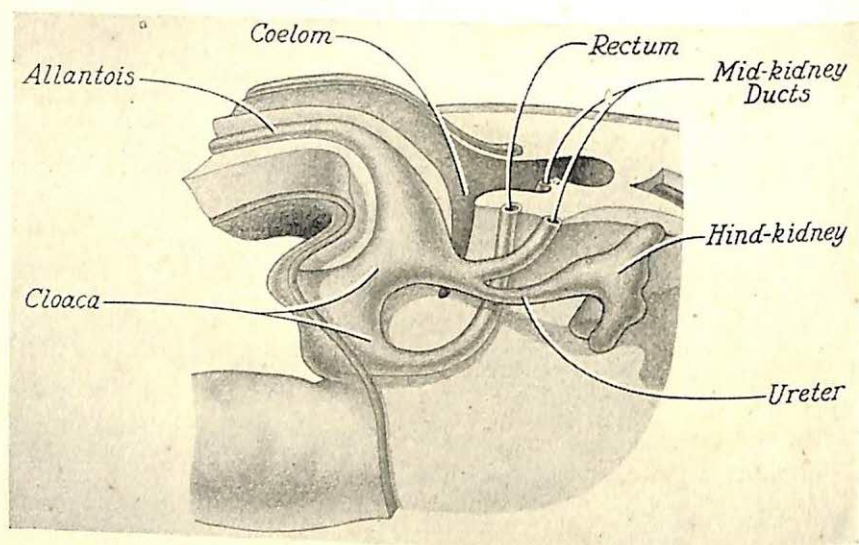


FIG. 86. Development of the hind-kidney and ureter, at about six weeks. Magnification about 30 diameters. (Redrawn with modifications from Arey's *Developmental Anatomy*, Prentiss, after Keibel. Courtesy of W. B. Saunders Company)

hind-kidney is chiefly in the enormous increase in number of the tubules and in their more compact arrangement, which simplifies the problem of distributing the blood to them and of carrying off the urine.

The bladder and urethra

The cloaca is partitioned off from the hind-gut in the seventh week of development (Fig. 87). Of the allantoic portion, the upper part, beyond the point where the mid-kidney ducts and the ureters enter, becomes the *urinary bladder*. The lower part, which serves as a duct to carry off the urine and, in the male, the sex cells, is the *urethra*. This opens, at first, on the underside (posterior) of a hump, or tubercle, that begins to grow out from the body just in front of the tail. The further development of this region will be considered later along with the development of the reproductive organs.

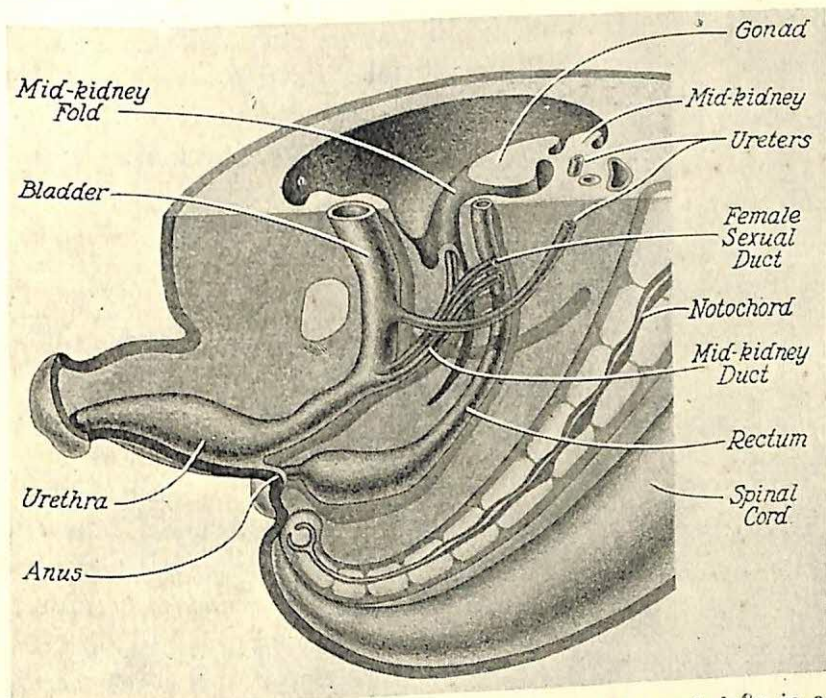


FIG. 87. Relations of the urinary bladder, urethra, and sexual ducts in a human embryo of nine weeks, following division of the cloaca. Magnification about 19 diameters. (Redrawn with modifications from Arey's *Developmental Anatomy*, Prentiss, after Keibel. Courtesy of W. B. Saunders Company)

ADEQUATE PERCEPTION OF ONE'S SURROUNDINGS—THE SENSE ORGANS

Circulation, digestion and absorption, respiration, and excretion—these activities are immediately concerned with the vital supply of energy and materials for the organism. We need also to be continually aware of changes in our environment, so as to make appropriate adjustments, secure food and water, protect ourselves, find a mate, enjoy living. The sensory receptors that make these activities possible must all be provided for before birth, although we must learn thereafter how to interpret what they tell us.

We probably think that we depend chiefly on sight and

hearing, but we would be in a worse way without an adequate sense of equilibrium, of directional movement, or of muscle tone (the degree to which each muscle is contracted). Pain is an efficient guardian, and the more specialized senses of heat, cold, and pressure assist in avoiding injury. Hunger and thirst are potent reminders of nutritive needs. Taste and smell provide discrimination and warning as to food and drink. All these have their special sense organs.

The sense organ of pain is the simplest, being merely a branched nerve-ending. The organs of heat, touch, and cold have bulbs of connective tissue around branched nerve-endings, increasing the range of their sensitivity. All of these are widely but unequally distributed over the body. They are especially concentrated in the hands and fingers. On the palms and finger tips, as in similar locations on the feet, the skin produces fine ridges which are so individual in character that we can be identified by them. Even identical twins have different fingerprints, a good indication of the ever-present differences in environment in which our genes must operate.

On the tongue grow taste buds, little groups of cells sunken under the surface, each equipped with a tiny hair. Different areas of the tongue become predominantly sensitive to different tastes, sour, sweet, salty, bitter. We may conjecture that there are four different kinds of taste buds, and that their distribution accounts for the various taste areas on the tongue.

While we are largely ignorant as yet of the genetic factors back of these taste and odor discriminations, it has been found that some 30 per cent of our population cannot taste phenyl-thio-carbamide at all, although to the remainder it has an intensely bitter taste. This instance of taste blindness is due to a recessive gene. More recently it has been discovered that there are a number of different taste reactions to mannose, a sugar, and these too are inherited.

Ciliated sensory cells are also produced in the nose. These are amazingly delicate in the perception of certain odors, and

the variety they can distinguish seems to be well-nigh unlimited.

The eye

The paired eyes begin as stalked outgrowths, or vesicles, from the underside of the forebrain.⁷ When each outgrowth reaches the skin, it forms a cup, and acts as an organizer for the ectoderm lying over it. The latter makes a little pit corresponding to the cup. Next, the pit closes over, and thus a little hollow ball of ectoderm is left. The cup develops into the *retina*, and the ball becomes the *lens* (Fig. 88).

In its specialization, the retina becomes differentiated into quite a number of layers. In the deepest layers are odd-shaped cells known as *rods* and *cones*, while the surface layers are made of nerve cells whose long projections extend over the surface of the retina to the origin of the *optic nerve*, in which they mount to the brain. The rods and cones are the special cells which are light-sensitive. The rods are distributed over the entire retina except at the very center, while the cones are absent around the rim. Both are lacking where the optic nerve enters—this is a blind spot. The rods are more responsive to faint light but cannot distinguish colors, so that in twilight or moonlight, when we see solely through the responses of the rods, objects are poorly defined and color is lacking. The cones provide us with our most distinct vision, and can discriminate between the three colors, red, green, and violet, of which all others are mixtures. (There are probably three distinct kinds of cones, each with maximum sensitivity for one of the three primary colors.)

⁷ In addition to the pair of functional eyes, man possesses the vestige of a primitive third eye, originally located on the top of the head, where an eye would have been useful to primitive vertebrates living on the ocean floor. This vestige is the *pineal body*, a small outgrowth from the forebrain (see Fig. 102). Some lizards still have a pineal eye, with lens and retina, buried beneath the skin. In man, the pineal body has not been shown to have any functional value, although it has been suspected of being a gland. The great French philosopher and mathematician Descartes thought it might possibly be the seat of the soul.

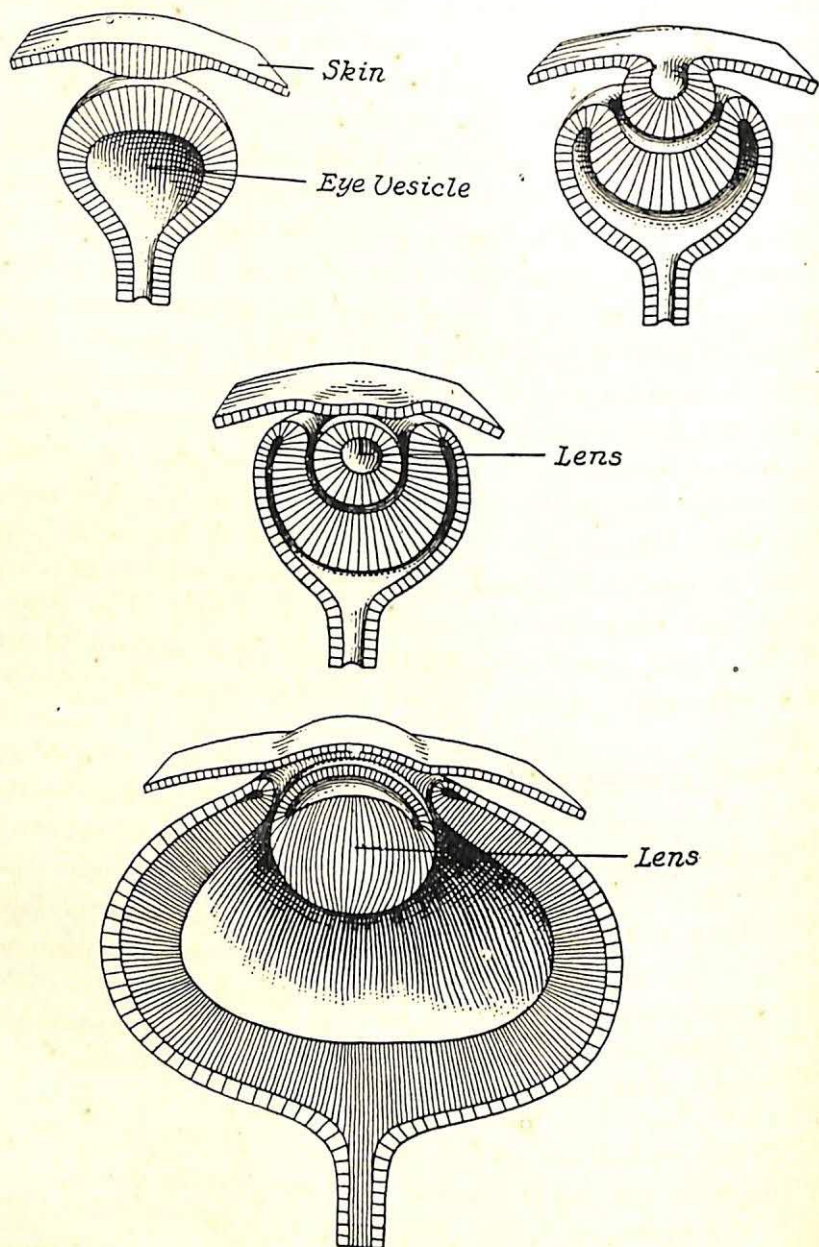


FIG. 88. Stages in the development of the retina and lens of the eye. (From Goldschmidt's *Ascaris*. Courtesy of Prentice-Hall, Inc.)

The retina, with the lens, secretes the jelly, the *vitreous humor*, which fills the hollow of the eyeball, and helps to keep it in shape and the retina in place. The part of the outer layer of the optic cup lying behind the retina becomes a thin layer which accumulates quantities of a black pigment that absorbs light, preventing its reflection and any consequent blurring of the image. From the rim of the optic cup there form the *ligaments which suspend the lens* and the major portion of the *iris*, including its pigmented layers and the radial and circular muscle fibers which respectively dilate and constrict the *pupil*—the hole in the center of the iris.

During development the lens gradually changes from a hollow to a solid ball. This is accomplished by the elongation of the innermost cells, as shown in Fig. 88. The inner cells thus become the transparent fibers of the lens. The blood vessels which supply the lens during its early development have degenerated completely by birth. The course of the large vessel that supplies the back surface of the lens is marked by the *hyaloid canal* through the vitreous humor.

The lens of the eye is a light-collecting device, bringing all the light entering the eye from any one source to a focus at a single point on a sensitive screen, the retina. No image could be formed without a lens, unless the entrance of light were limited to a pinhole in size, and then the amount of light that could enter would generally be too faint to stimulate the cones and, perhaps, even the rods of the retina. We would certainly see no gorgeous colors; everything would be dim as in faint moonlight. In animals like the flatworm, in which we find eyes, but no lenses, there can be no real vision whatever, for no images can be formed. The worm is merely sensitive to varying degrees of light and darkness.

In the human eye, the lens is not the most powerful light-gatherer (see p. 293). It is, nevertheless, of prime importance in vision, for it furnishes the means whereby we accommodate for distance, that is, whereby we focus our vision for

objects close to us or far away. This is accomplished by an actual change in the shape of the elastic lens. When the fibers suspending the lens become looser, the lens becomes rounder and focuses on near-by objects. When the suspensory fibers become taut, the lens is pressed flatter and distant objects are brought into focus. Very quickly during the growth of the eyeball, the lens is brought to just the proper distance from the retina to cast the image onto the latter.

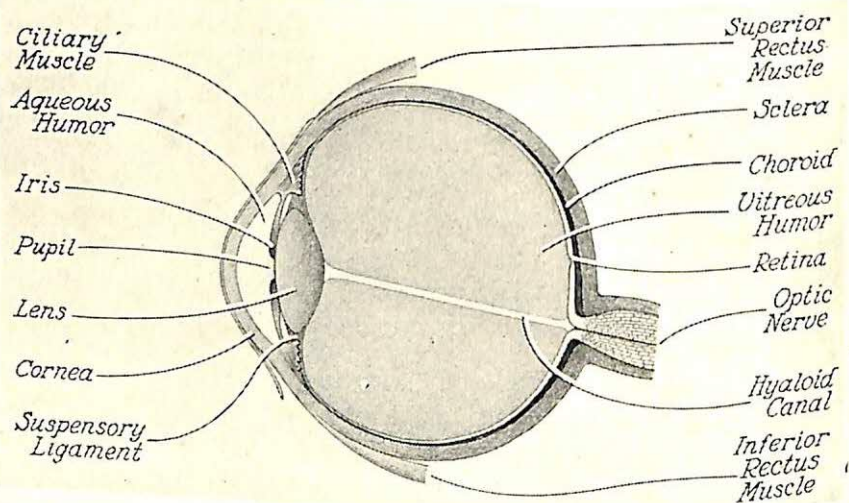


FIG. 89. Diagrammatic section through the mature human eye. (Redrawn from Buchanan's *Elements of Biology*. Courtesy of Harper and Brothers.)

One thing about the image should be noticed; it is completely inverted. Experiments show that we do not inherit a mental ability to reinvert the picture of what we see, but that we must learn to do it through experience. Small wonder that babies grope so wildly at first! To learn this for the first time must be quite a task.

The rest of the eye (see Fig. 89), except for a thin outer membrane (*conjunctiva*) that is continuous with the eyelids, comes from the mesoderm. This forms two coats around the retina and lens and, in addition, produces the voluntary

muscles which move each eye and pass from the eyeball to the bony socket.

The inner mesodermal layer, next to the retina, is called the *choroid coat*. It is rich in the blood vessels which supply the eye. In front this layer contributes to the iris and the ciliary muscles. Owing to the manner of their attachment, contraction of the ciliary muscles loosens the suspensory fibers of the lens, and when the ciliary muscles relax, the suspensory fibers tauten.

The outer coat of the eyeball is the tough white *sclera*, originating, like the choroid, from the mesoderm. It is the part we see in front as the white of the eye. Just over the iris it becomes transparent, and this portion is known as the *cornea*. It is lens-shaped and in man is more powerful than the real lens in gathering light. Also, being very tough like the rest of the sclera, it provides excellent protection. Between it and the lens a watery fluid, the *aqueous humor*, accumulates, serving to prevent the refraction that would occur were the space air-filled, and that would decrease the power of the lens.

Blindness results whenever the cornea becomes opaque. Congenital blindness (due to gonorrhea) is of this sort. The germ of this disease attacks the membranes of the vagina and the cornea by preference, and many a child is blind from birth on account of infection from its mother. There is no excuse for this today, as it is well known that a few drops of a silver nitrate or similar solution in the eyes of a newborn babe will effectually sterilize them. Most states in our country now require this by law.

The ear

The ear (Fig. 90) is really double in origin. The inner ear, the true sense organ, is formed from a pocket of the ectoderm overlying the brain. It later becomes buried deep within the skull. The remainder of the ear is an accessory to hearing and represents the salvage of various gill structures.

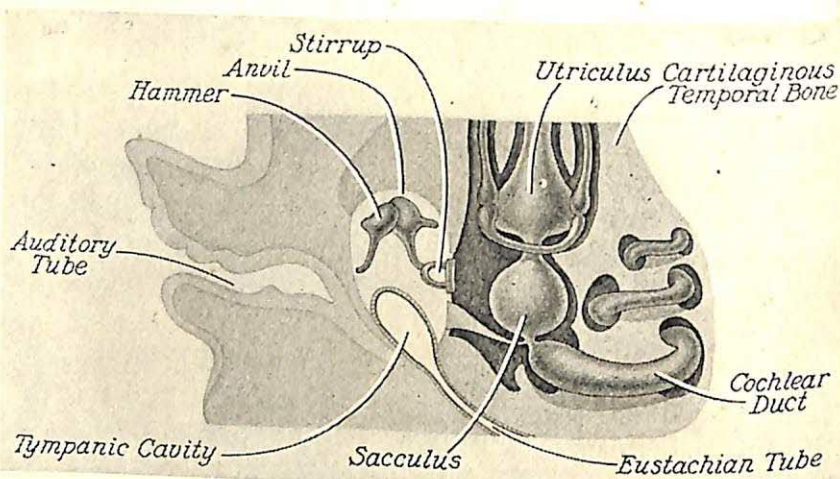


FIG. 90. The relations of the developing internal, middle, and external parts of the fetal ear at three months. The spongy tissue around the bones of the middle ear has yet to degenerate to produce the ultimate enlargement of the tympanic cavity of the middle ear. (Redrawn with modifications from Arcey's *Developmental Anatomy*. Courtesy of W. B. Saunders Company)

As related before, the first gill pouch becomes the *Eustachian tube* leading from the throat to the eardrum. The corresponding external cleft becomes the *auditory tube*, and the membrane between them is the *eardrum*.

Around the opening of each auditory tube arise six little bumps (Fig. 91, 1-6) and a curving ridge (Fig. 91*A*, *af*). These grow together to make the external ears. These superficial adornments should presumably function as an aid to hearing, as funnels to collect sound waves and reflect them in toward the drum. Actually their value in man is negligible. One can hear practically as well with no external ears at all. If this is so, then what must one think of the presence of a complete set of muscles connecting ear and skull, capable only of wiggling the ears, and that only in an occasional person? Or of the internal muscles of the ear, which could cup our ears the better to pick up faint sounds, if only they were stronger and had functional nervous connections? The same muscles are wonderfully useful to a

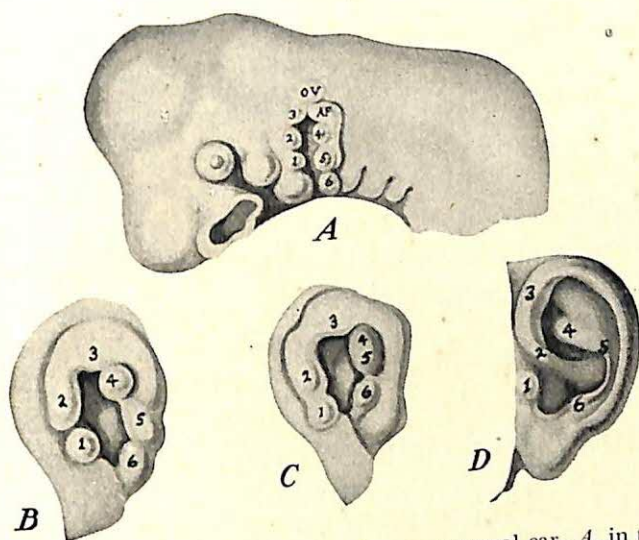


FIG. 91. Stages in the development of the human external ear. *A*, in the sixth week (*ov*, the inner ear). *B*, *C*, during the seventh week. *D*, adult. (Redrawn from Arey's *Developmental Anatomy*, after His. Courtesy of W. B. Saunders Company)

donkey, and presumably in us must represent a heritage from some ancestor with bigger and better ears than ours.

Within the cavity of the middle ear (that is, beneath the eardrum) there develop three little bones of peculiar shape (see Fig. 90). They are derived from the cartilaginous gill bars, which form in the flesh between the gill clefts, and which are quite essential, in fishes, for the support of the gills. Each of these gill bars is V-shaped, hinged at the apex, which points toward the rear. From the pair in front of the first cleft come the upper and lower jaws, the right and left sides of each growing forward until they meet in front. In the long-jawed fishes, amphibians, and reptiles, these jaws retain their original joint with the skull; but, along with other mammals, human beings form a new one farther forward where the contraction of the jaw muscle has more favorable leverage, and can exert greater speed and power in snapping shut or clenching the lower jaw. This leaves the rear half of

the primitive jaw useless, and most of it never turns to bone. But the very tips of the upper and lower jaws, at the original joint itself, lie close to the ear and are turned to a new use. They develop into the *hammer* and *anvil*, the first two of the chain of three little bones which bridge the middle ear and convey vibrations from the eardrum across to the inner ear. The third little bone, the *stirrup*, comes from the second gill bar, which in fishes braces the joint of the jaws against the skull. In amphibians and reptiles the upper jaw has become fused to the skull, and this service is no longer needed. Being conveniently placed, this gill bar was then utilized as the first earbone, originally stretching all the way from the eardrum to the opening of the inner ear.

These three little bones play a part in intensifying the vibrations, for they transmit them from a large membrane, the eardrum, to a small one at the oval window of the inner ear. Calculations show that this magnification is about ten times. The middle ear is thus a valuable aid to hearing. Up until the last fetal months, however, the spongy connective tissue in which the three little bones develop still fills the upper part of the chamber of the middle ear, as can be seen in Fig. 90. This material must degenerate and free the movements of the bones before hearing can become acute. Since this process is not completed until after birth, newborn infants are deaf for some weeks.

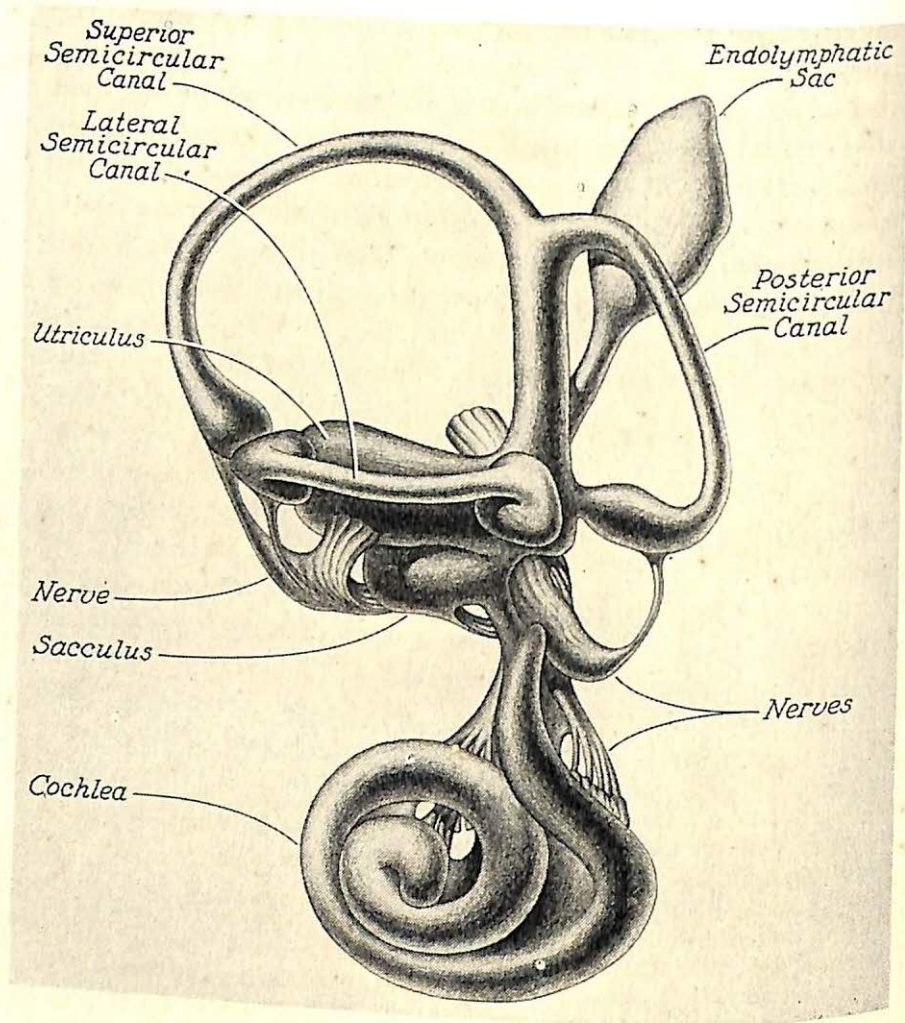
The Eustachian tube is helpful in equalizing the air pressure on both sides of the eardrum, thus preventing it from bursting. The middle ear has its disadvantages, however, since its connection with the mouth lends itself to infection, especially in babyhood when the passage is still very short. Not only is the middle ear itself an ideal haven for germs, but it lies close to the hollow mastoid bone of the skull. Infections may spread to these air spaces, setting up painful inflammations that can be dealt with only by a delicate and dangerous operation, shaving or clipping away the bone until

the cavities are exposed, and then draining and sterilizing them.⁸

The inner ear is a series of membranous sacks and canals, all filled with fluid and lying imbedded in the skull (Figs. 90, 92). At first the inner ear is just a single sack, from which various outgrowths later emerge. The *endolymphatic duct* and *sack* are the vestiges of the original connection of the inner ear with the outer surface of the head. At the upper end of the central sack three disks grow out, each in a different plane, so that each is roughly at right angles to the other two. These disks grow thinner in the middle, and finally become hollow rings, the *semicircular canals*. This most primitive part of the ear is concerned not with hearing but with a far more essential sense, that of equilibrium. At the base of each ring is a swollen bulb, lined with sensory cells bearing cilia. When the head moves in any direction, the inertia of the fluid in the canals causes it to produce pressure in a particular direction upon these sensory "hair cells." Their excitation is transmitted over the auditory nerve to the brain and there combined into an interpretation (perception). Since each semicircular canal occupies a plane of space at right angles to the two others, any movement will affect one or more of the canals.

The original central sack also becomes enlarged and partly separated into two, an upper *utricle* and a lower *sacculus*. These, too, are sense organs of equilibrium, assisting the canals by informing us of the position of our heads even when they are still. In each of these chambers there is a cluster of "hair cells," and clumps of little "ear stones" (*otoliths*) of limestone attached to the hairs. In the utricle the stones press vertically on the hairs; in the sacculus they hang laterally, producing a shearing pull upon them. Any change in the position of the head, therefore, alters the pressure or pull

⁸ Recently word comes that the new sulfa drugs, already proved of great value in the treatment of so many ailments, may render these stern measures less frequently necessary.



A

FIG. 92. For B see p. 299.

of the stones on the sensory cilia, and keeps us informed as to "which end is up" (Fig. 92B).

From beneath the central sack there grows a long slender pouch, which coils at the tip until it looks like a snail shell. This is the *cochlea*, the real sense organ of hearing. It is rudimentary in fishes and amphibians and becomes coiled only in mammals. When its development is completed, the

coiled cavity is divided internally by membranes into three passages, the original or central one closed off, the upper and lower, formed subsequently, communicating at the apex of the coil. All three are filled with fluid. Into the upper passage, the *vestibular canal*, opens the oval window against which the stirrup fits, so that vibrations of the latter are transmitted to the fluid in the passage. They then pass up to the apex of the coil and back down through the lower passage,

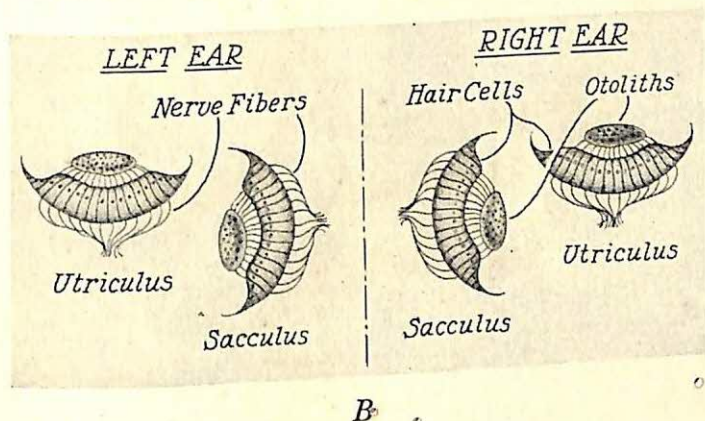


FIG. 92. *A*, the inner ear. Redrawn with modifications from Buchanan's *Elements of Biology*. Courtesy of Harper & Bros. *B*, the sense organs of static equilibrium in the inner ear. A stimulus is exerted upon the hair cells through the pull of gravity upon the otoliths attached to the little hairs. Tilting the head to left or right acts upon the sacculi of the two ears in an opposite way. Tilting the head forward or backward, or turning upside down, acts upon the utriculi. (Redrawn from Carlson and Johnson's *The Machinery of the Body*. Courtesy of The University of Chicago Press)

the *tympanic canal*, ending at a little round window covered with a membrane, which takes up the vibration, preventing its being echoed back. If the coil of the cochlea were straightened out, it would appear as in Fig. 93.

Separating the lower passage from the central enclosed one is the *basilar membrane*. Upon it rests a layer of sensory hair cells, firmly supported by skeletal rods, while above them hangs the *tectorial membrane* supported from one side. One

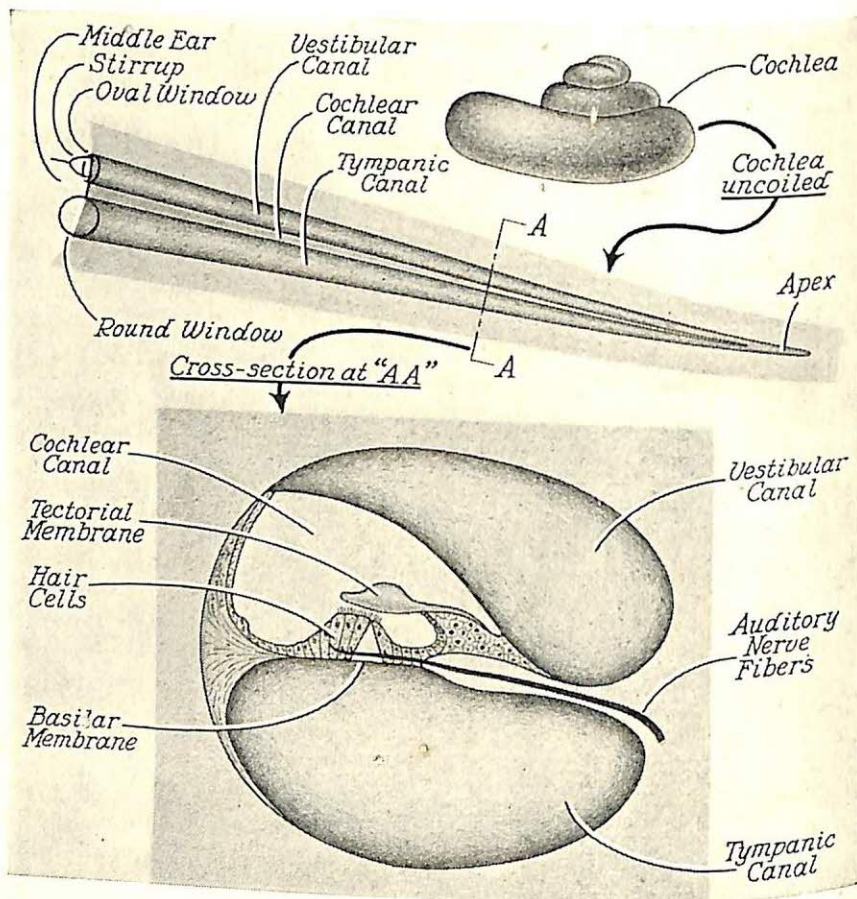


FIG. 93. The organ of hearing. "Uncoiling" the spiral cochlea and making a cross section of it to reveal the relationships of its three canals. (Redrawn from Carlson and Johnson's *The Machinery of the Body*. Courtesy of The University of Chicago Press)

widely accepted theory of hearing is that when the basilar membrane is thrown into vibration, these cells bob up and down, and the cilia are bumped against the overhanging membrane. At any rate, the hair cells are thrown into a state of excitation, and their stimulation is transmitted to the brain and interpreted as sound.

The basilar membrane is tuned somewhat like a stringed instrument to sounds of various *pitch*. At the tip of the coil

it is broad and at the other end narrow, varying gradually between, so that at the tip, like a long string, it responds to a deep tone, and at the other end, like a short string, to a high tone. Development proceeds from the base to the tip of the coil.

In the ear, a vibration of a particular frequency (number of waves per second) in the fluid of the lower passage sets the basilar membrane vibrating only at the point that is tuned to it. The stronger the vibrations, the more the sensory cells at the tuned level of the basilar membrane will be stimulated. In this way we hear some sounds faintly, and others loudly.

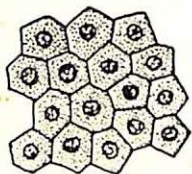
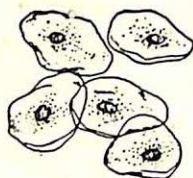
The timbre, or tone color, of a sound is really due to a combination of tones. Whether or not this combination seems pleasing (harmonious) depends partly on certain mathematical relations between sound frequencies (multiples, for instance, are harmonious) and partly on learning.

ADEQUATE PROVISION FOR ADJUSTMENT

The skin and its glands

The skin is a protection of no mean sort. The *epidermis*, or outer layer (Fig. 94, *epithelial cells*), is a specialization of the ectoderm. Underlying cells divide rapidly and the outer ones become horny and flatter and flatter as they are pushed to the outside. They soon die, and only their flattened horny shells remain to protect our living cells from injury.

The *nails* and *hairs* are special horny outgrowths of folds in the epidermis. Only primates (monkeys, apes, and man) have flat nails, although other mammals have claws, hoofs, or horns which are similar products of the skin. Hair is common to all mammals, the finer grades, fur and wool, proving useful to us in supplying our own relative lack. Like other mammals, we too develop a complete coat of hair, but this is shed from our bodies during the last month before birth.



Types of Epithelial Cells



Striated Muscle



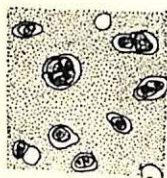
Plain Muscle



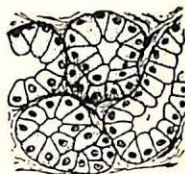
Bone



Connective Tissue



Cartilage



Gland Tissue

FIG. 94. Various types of tissues. (From Buchanan's *Elements of Biology*. Courtesy of Harper & Brothers)

Hairs grow from columnar *follicles* in the skin. Each follicle has a little muscle attached to it, capable of erecting it (or, in our naked poverty, of making goose pimples). There is a nerve wound around each one, too, so that any movement of the hair can be perceived as a sensation of contact. Each follicle also has a side pouch of gland cells which secrete an oil that keeps the hair from becoming brittle and lubricates the skin.

The sweat glands, another feature limited to mammals, are also pockets of epidermis pushed deep into the dermis. Here the secretory cells are in close contact with capillaries, from which they filter off water carrying a small amount of dissolved salts. Their rate of secretion is controlled by the auto-

onomic nervous system, or by adrenalin. The regulation of the evaporation of perspiration is one of the principal means by which we maintain our body temperature constant and so are able ultimately to control our activity regardless of season, climate, or weather.

The mammary, or milk, glands are also specializations of the epidermis. In fact they probably are modified sweat glands, for in the lower mammals they have the same structure as certain large specialized sweat glands. At six weeks a "milk line" or ridge appears along each side of the body between the front and rear limb buds. Soon all but the anterior one third of this disappears, although in various other mammals paired glands arise the entire length of the lines, and even in man there are sometimes extra pairs. The nipples are formed shortly before, or even after, birth.

The deeper layer of the skin is formed from mesoderm; it is the *dermis*. Richly supplied with nerves and blood vessels, it is the seat of skin sensation. Its abundance of connective tissue makes the skin elastic and flexible, while other cells store up fat in a layer that is good insulation against heat and cold.

The muscles

Muscle cells specialize in movement. We have three types, all of which come from the mesoderm. Some muscles are made of spindle-shaped cells fastened to one another in sheets (see Fig. 94). The peristaltic and constrictive movements of the stomach and intestines in controlling the passage of food through the digestive tube, the constriction of the urinary bladder in voiding urine and of the uterus in menstruation and labor, and the constriction of the blood vessels that regulates the amount of blood flow to each part of the body, are movements of these muscles. They cannot be controlled by the will, as a rule, and are therefore called *involuntary*. (This is the most primitive kind of muscle cell, for it is the only sort found in worms. Striped muscle cells are

found only on the more advanced level of the crustaceans and insects, as well as among the chordates.)

Heart muscles consist of muscle cells which have numerous interconnections, which make them almost one great continuous muscle cell. They have a spontaneous tendency to contract rhythmically, even when removed from nervous stimulation, as when growing isolated in a tissue-culture. Although involuntary, they show crossbands, so that they are intermediate in character between primitive "smooth" muscle and the voluntary muscles.

The muscle fibers of the voluntary muscles are banded with cross-stripes. Each fiber is really a composite of a number of cells, the nuclei of which are studded over the surface of the fiber (see Fig. 94). Like all muscle cells, when such a fiber contracts it thickens and shortens; its volume does not actually change very much.

The voluntary muscles of the trunk come from the original paired segments of the mesoderm, which quite early fuse together until nearly all trace of the segmentation is gone, and later, in quite a variety of ways, keep changing direction, splitting and fusing, degenerating and even migrating, until the muscles are produced. Extending up the back of the neck to the skull, these segments supply even the eye muscles. But the muscles of throat, face, and jaws come from the gill muscles. The facial muscles which are responsible for our expressions of emotion are paralleled in other mammals by numerous superficial skin muscles which can twitch the skin over the whole body.

The limb muscles make up the bulk of our arms and legs and, in addition, form a considerable amount of the overlying parts of chest, back, and loins. The limb buds first appear toward the end of the fifth week of development, the upper ones slightly in advance of the lower. Into these buds, one pair on a level with the heart, the other just in front of the tail, there migrate unspecialized mesodermal cells. The outer ends flatten into little paddles, constricted off from

the basal portions, and five lobes appear on each of them. By the end of the eighth week, these are molded into recognizable fingers or toes, and the divisions of the limbs are clear-cut (Fig. 95).

Within the developing bud, the mesodermal cells commence to specialize, central ones becoming cartilage cells

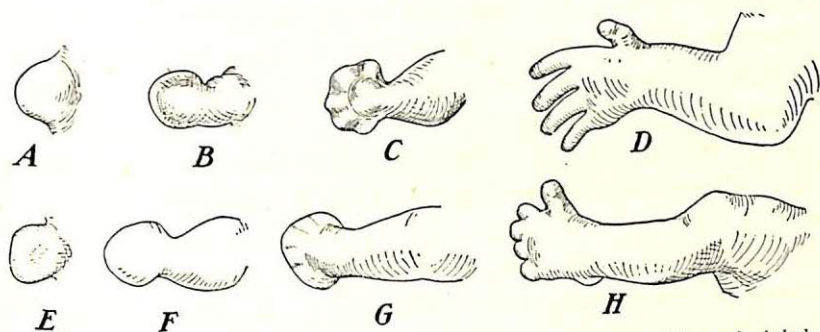


FIG. 95. Stages in the development of the limbs between the fifth and eighth weeks (magnified about 5 diameters). Upper row, hand and arm. Lower row, foot and leg. (From Arey's *Developmental Anatomy*. Courtesy of W. B. Saunders Company)

and forming a core of cartilage, those around this core becoming muscle cells. The muscle fibers are bound together in bundles by developing sheaths of connective tissue, and at the ends of each muscle these sheaths are fastened firmly, as tough tendons, to the skeletal structures which are now becoming bony. Nerves, too, grow down into the limb, then branch, and connect with each fiber. By ten weeks, the first feeble movements are beginning, and thereafter a new element enters into the development of the muscles. No longer purely automatic, gene- and enzyme-controlled, *growth and development are from this time on modified by use*. Practice stimulates development along lines of use, and movements become not only more powerful but less clumsy, more delicately controlled.

The muscles of the limbs are in two sets, which work in opposition to each other. This is necessary, since a muscle

can do, work only by pulling while it is contracting, and accordingly a different set of muscles must be supplied for counteraction. All of these muscles are located at least one joint closer to the body than the part they move. This arrangement is demonstrably more efficient than a more distal one would be. The muscles which move the whole arm at the shoulder are thus on chest and back, and those which move the leg at the hip are similarly on the trunk. These develop first, then those of upper arm and thigh, next those of forearm and calf, and finally those in the hand and foot. *Development regularly moves from center to extremities just as it does from the head toward the tail.*

The skeleton

Most of us think of the skeleton as of use purely in protection and support. These functions, to be sure, are important, but support itself is only an adjunct to movement. *The primary function of the skeleton is the part it plays in movement. The voluntary muscles produce movements by pulling bones into varying positions at their joints.* This makes necessary firm connections between the bones. These connections are provided by *ligaments*, tough strands of white connective tissue (see Fig. 94). The joints, too, must work smoothly, without friction. The ends of the bones at a freely movable joint are covered with cartilage, the ligaments form a sack completely enclosing the joint, and fluid within this sack acts as a lubricant, keeping the cartilage soft and slippery.

The skeleton of the head and trunk (axial skeleton) centers around the *backbone*. This begins as a clumping of mesodermal cells around the notochord. Each of these secretes a clear, translucent product, *cartilage*, around itself, a stuff elastic and smooth but not very rigid (see Fig. 94). Later specialization (after the seventh week) results in *bone* cells (see Fig. 94). These produce elastic fibers like less specialized connective tissues, but they go further by depositing

around the fibers salts of calcium, mostly carbonate-phosphate. This mixture provides great strength and rigidity, while cartilage is maintained where flexibility is more essential. In each segment the bone cells crowd in and supplant the cartilage around the notochord, leaving a pad of cartilage between every two blocks of bone, or *vertebrae*. From each vertebra there grows up an arch completely roofing over the spinal cord and protecting it. The adjacent muscles of the back become attached to a spine projecting from this arch, as well as to the body of the vertebra. Projections from the vertebra on each side form bases for the ribs, while a couple sticking out in front and a second pair behind make articulations with the *vertebrae* fore and aft.

The *vertebrae* do not all become exactly alike. Those in the neck stay relatively small, but grow huge spines for the attachment of the neck muscles which move the head and the back muscles which move the neck. The two at the very top are modified into a kind of ring and pivot joint for firmly supporting the skull and yet permitting the head to move freely. The thoracic (chest) *vertebrae* alone carry typical ribs in man, although in other animals these extend much farther down the spinal column. Five *vertebrae* in the pelvis become fused together to form a firm support for the bony girdle to which the legs are attached (this is the *sacrum*). And below that are the three or four remnants of our tail—the *coccyx*.

One should notice, too, the curves of our backbone (Fig. 96). The upper one corresponds to the arch of the spinal column which, in horizontal quadrupeds, enables it better to support the weight of the trunk suspended from it. But the reverse curve, in the region of the loins, or lumbar region, is a specialty of man. Without it we could not stand upright, as the upper curve would throw our center of balance too far forward. This is why the anthropoid apes must stoop—they lack a reverse curve which would bring their center of grav-

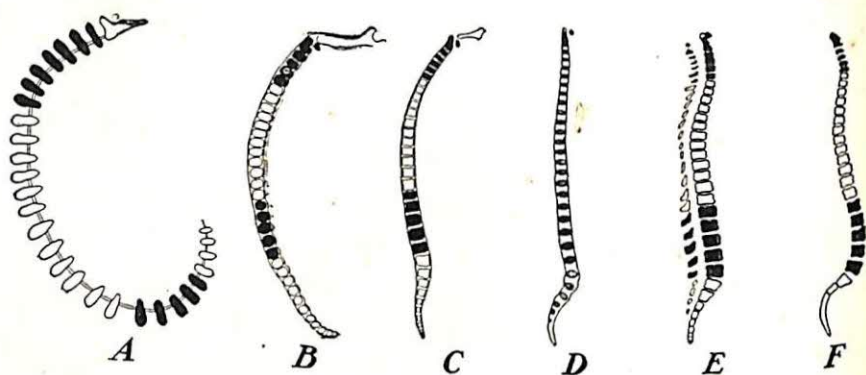
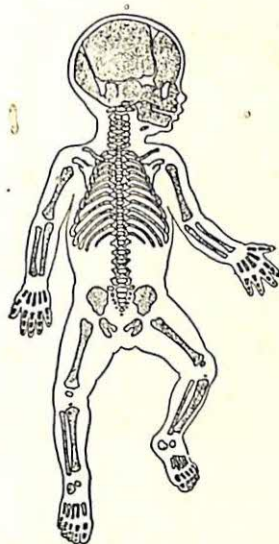


FIG. 96. Spinal curvatures at various ages, viewed from the right side. (From Arey's *Developmental Anatomy*, after Peters. Courtesy of W. B. Saunders Company)

ity back over their hips. Now these curves are not present even at birth, the backbone being still in the form of a simple arch. The weight of the body and the pull of muscles as an erect position is finally assumed are thought to be necessary to bring them out.

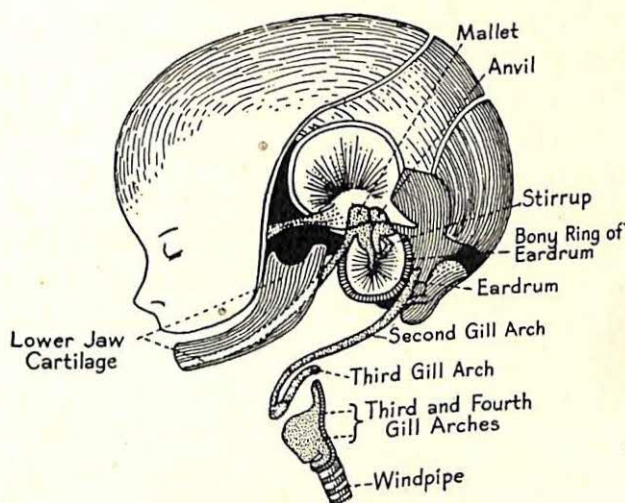
The *skull* is formed of many bones which gradually fuse together. The *cranium*, that part which encases the brain, is not all cartilage to begin with. While the back, base, and temples are first present as cartilage that is later transformed into bone, the bones that cover top and forehead are formed in the membranes that cover the brain (Fig. 97A). They gradually spread out until they meet, but even in the infant there are still "soft spots," parts of the membrane into which they have not yet extended. As the bones of the cranium lengthen, they meet and interlock like pieces of a jigsaw puzzle. Gradually even these seams are obliterated, and in an old person the cranium is a single sheet of bone. Thus the approximate age of a person at death can be read from his skull.

To the cranium are fastened the facial bones which either begin as capsules of cartilage enclosing the inner ear and



A

FIG. 97. A, the bony skeleton at birth. (From Arey's *Developmental Anatomy*, after Scammon and Hess. Courtesy of W. B. Saunders Co.) B, the skeletal derivatives of the gill arches. (From Goldschmidt's *Ascaris*. Courtesy of Prentice-Hall, Inc.)



B

olfactory (smelling) organs, or form from membranes—the cheek bones, the bridge of the nose, and most of the eye-socket. Parts of the nasal cartilages, of course, never turn to bone.

Other skeletal parts of head and neck come from parts of the cartilaginous gill bars (Fig. 97*B*). The first pair of these is covered over and replaced by bones from the skin, making a right and left upper and lower jawbone. The bony replacements form a new jaw joint in front of the ear, and the old joint, as we have seen, is cut off and left to transmit sound across the middle ear. The jawbones grow forward until they meet and fuse in front. (That is, they do normally. Mutant genes responsible for failure here are variable in expression, resulting in cleft chin, cleft palate, or harelip. These defects may be fatal or, when mild, merely disfiguring.) The bony palate similarly appears as two flat pieces of bone that grow across from the upper jaws until they meet, separating the nasal cavity from the mouth in front but leaving them connected farther back.

As we have already observed, the upper end of the second cartilaginous gill bar develops into the stirrup, the third of the bridge of little bones across the middle ear. The lower part of the bar also becomes bone, a part of the hyoid bone which supports the base of the tongue. The rest of this bone comes from the third pair of gill bars. The fourth and fifth pairs remain cartilage, and are expanded and modified into the cartilages of the larynx, to which the vocal cords are attached. On the whole, then, a number of parts of the gill bars find some later use, but other parts are formed only to degenerate.

The ribs grow out from the vertebrae, become cartilage, then bone. Those in the neck are very short and are fused with the vertebrae. Then come the twelve pairs of regular ribs, curving around the chest. The front portions of these where they connect with the breastbone, remain cartilagi-

nous, and the breastbone (or sternum) is itself not completely transformed to bone. The two lower pairs of ribs never become attached and remain "floating" in front. The next group of vertebrae have short ribs fused into them, while the fused vertebrae that make up the sacrum (Fig. 98) have fused rib projections which help to make an adequate support for the rest of the pelvis.

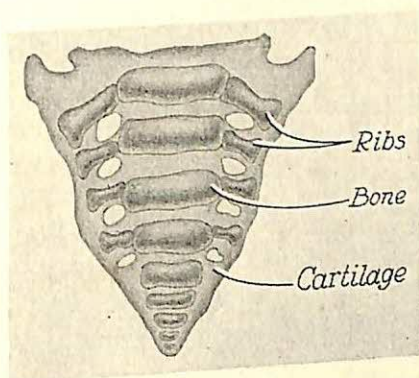


FIG. 98. An early stage in the development of the sacrum and coccyx. The ribs appear only on the four sacral vertebrae.

The limbs are fastened to two girdles, the shoulder girdle and the pelvis. We should note that in all the higher animals, from certain fossil lobe-finned fishes on up the scale through amphibians and reptiles to birds and mammals, the limbs and their girdles are built on the same plan. Bone for bone they correspond, with only minor modifications in size and shape or number of digits. The fins of lobe-finned fish, the legs of a frog or lizard, the wings and legs of a bird, the paddles of a whale or the flippers of a seal, and our own arms and hands, legs and feet, are homologous structures, although adapted to various uses. *This must surely mean that the primary genes concerned with the nature of limb development are the same in all the members of this group, although secondary genes have become different through mutation.*

The *pelvis*, bony girdle to which our legs are attached, is

rigidly fixed to the sacrum, but our arms are fixed to a shoulder girdle resembling those of other mammals whose forelegs must take the full impact of their body weight in running and landing after a leap. The great bone of the upper arm, the *humerus*, is attached most indirectly to the backbone. Its ball fits into a socket joint which allows the arm to move freely in all directions at the shoulder. This socket is provided by the shoulder blade (*scapula*), the large flat body of which lies imbedded between the shoulder and back muscles, which take up much of the shock of landing. Close to the shoulder joint, the shoulder blade is braced by a curving collarbone (*clavicle*), which is attached at its other end to the top of the *sternum* (breastbone). Among mammals the collarbone is well developed chiefly in those that climb, dig, or fly, while in running quadrupeds it is vestigial and the whole shoulder girdle is "floating." The two collarbones serve to brace the shoulder joints and allow considerably greater freedom of arm movement, but they are not strong enough to withstand the full shock of landing on the forelimbs, and are frequently broken. The sternum is connected with the ribs only by flexible cartilage, and the ribs themselves are shaped to serve as springs. Thus a mere fraction of the jar of landing reaches the backbone and is transmitted to the body as a whole. How different when we jump and land on our feet! Only a bit of the shock can be taken up by bent knees, and the rest of the force of impact sends tremors through our whole frame. It is impossible for us really to "land lightly on our feet." So far as our limb girdles are concerned, we are undeniably constructed to leap and land on all fours, but the rest of our anatomy fails to correspond. It has been modified to make possible an upright carriage, while the flexible attachment of the forelimbs, certainly no disadvantage to us, has been retained. (The front tip of the shoulder blade represents a vestige of a third bone—coracoid—of the shoulder girdle, present in other vertebrates. Like the collarbone, it braces the shoulder, connect-

ing with the lower end of the sternum. In our development, it gets only as far as a ligament, with a few bits of cartilage imbedded here and there along it. This has decreased the strength of the shoulder joint; but as we no longer practice landing on our forelimbs, it does not matter.)

At the elbow are two interesting joints. There are two bones in the forearm, the *radius* and the *ulna*, the latter on the same side as the thumb. A prong of the ulna slides in a groove in the humerus, making a hinge joint which acts as a final check on the movement produced by the triceps muscle when the forearm is extended. The radius has a flat disk-like upper end which pivots on the humerus, thus enabling us to turn our hands over. The two types of motion represented here emphasize the relation of joints to movements.

These long bones, together with those of the leg, are hollow in the shaft and spongy at the ends. This is the construction which, on engineering principles, is by far the strongest for a given mass and is for that reason used extensively in making tubular metal furniture. The cavity of the long bones is not waste space, however. The shaft is filled with yellow marrow, a store of fatty substances, and the cavities of the spongy bone contain red marrow, whence come the red blood corpuscles and other blood cells. The bone itself is not solid. Under the microscope, sections show many fine canals through which blood vessels and nerves make their way to still smaller cavities where dwell the single bone cells, imprisoned by their own product, and communicating with one another only by delicate projections. But this is so only in a fairly mature bone. Like most other parts of the skeleton, the long bones start out as clumps of mesodermal cells which turn to cartilage. After this has assumed the rough shape of the bone, centers of bone formation arise in and around it. As mineral matter is deposited, the cartilage is gradually surrounded by a shaft of bone, while within the cartilage itself spongy bone is formed. The cartilage degen-

erates, and along with it some of the spongy bone, and thus the marrow cavities are created (Fig. 99E, F.).

Growth must take place without interfering with the action of the joints. At first, bone cells replace the cartilage only in the shaft, and the ends are still formed of rapidly growing and readily modifiable cartilage (Fig. 99A-C). Later,

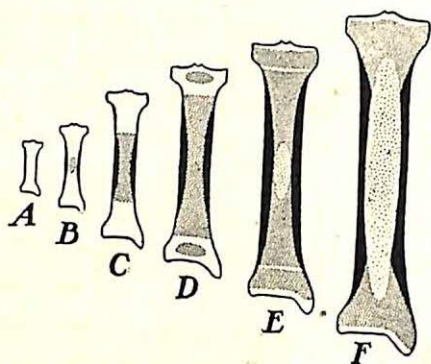


FIG. 99. Stages in the growth of a long bone. A, cartilage. B, C, spongy bone (stippled) being deposited within the cartilage and compact bone (black) being deposited around it. D, epiphyses appearing at each end of the bone. E, the marrow cavity (sparse stipple), appearing through degeneration within the spongy bone. F, epiphyses finally uniting with the shaft, leaving articular cartilage at each end. The marrow cavity is continuing to enlarge as more bone is deposited on the outside of the shaft. (From Arey's *Developmental Anatomy*. Courtesy of W. B. Saunders Company)

centers of bone formation appear also in the ends of the bones (Fig. 99D). Growth in the length of the bone thereafter takes place between these *epiphyses*, as they are called, and the shaft through a formation of new cartilage which is gradually transformed into bone. Most of the epiphyses do not appear until after birth, and many not until adolescence. During all this time, when shaft and ends are finally being fused, the calcium supply in the diet is a matter of great importance. At maturity, the shaft and ends are finally fused, and the bone stops growing in length. Growth in diameter of either the shaft or the ends is no problem—more bone is simply added on as a superficial layer, while the central

marrow cavity becomes enlarged by resorption of bone from within.

The pelvis is a complete ring of bone, except in front, where a small gap is closed by cartilage and ligaments. These provide some elasticity, which is especially important in childbirth. During labor, the babe must pass from its mother's uterus down through the vagina. This opens below the pelvic ring, and birth would be extremely difficult or even impossible if previous preparation had not been made. Some influence, perhaps a hormone, causes the ligaments here to relax during the birth process, allowing the pelvis to open up more broadly.

The leg bones, *femur* in the thigh, *tibia* and *fibula* in the shank, are similar to those in the arms, except that the fibula no longer pivots at the knee, but becomes fused to the tibia (shin bone) below the knee joint. Hence the knee is only a hinge joint. It is protected by the kneecap, a little floating bone formed within a muscle tendon.

The direction of the knee joint is, however, the reverse of that of the elbow. This again is interpretable in terms of the structure of other vertebrates. Primitive land animals had spraddled legs, with both elbow and knee directed outward. With increasing length of limb, the legs were drawn under the body where they supported it more effectively, so that the muscles were relieved of considerable work. This development involved rotation of the limbs, rotation which took place in opposite directions, the elbow facing backward, the knee forward. Although we as men no longer creep, crawl, or run on all fours, the rotation of our limbs indicates the ancestral condition, still retained by most mammals.

Concerning wrists and ankles, hands and feet, toes and fingers, volumes could be (and have been) written.⁹ The wonderful flexibility of the hand, with its opposable thumb, as

⁹ See especially the fine exposition by Sir Charles Bell, the noted nineteenth-century surgeon, on *The Hand*. This pre-Darwinian volume of the "Bridge-water Treatises," written to illustrate the power, wisdom, and goodness of God, is a great classic of anatomy.

controlled by our brain, has been an important, perhaps even an essential, factor in our upward rise from savagery. Yet the monkeys and apes are better equipped in this respect than we, for they are four-handed. The use we make of our hands is evidently even more a matter of the intelligence that controls them than of their own inherent powers. It is really in the feet that we are unique. Bone for bone and muscle for muscle, the structure of the human foot corresponds to that of the lower "hand" of an ape. Yet our greatly shortened toes and relatively huge big toe on the inside have been drawn into line, and the big toe has lost most of its opposability. Together with the big heel bone that now touches the ground and the increased arch and rigidity of the instep, these are modifications of the primate "hand" that have made possible our erect carriage and have freed our own hands for manipulation.

ADEQUATE PROVISION FOR COORDINATION—THE NERVOUS SYSTEM

The appropriateness of our responses depends upon the existence of pathways for transmitting impulses from the excited sense organ to the muscle or gland cells which are our means of response. These pathways, potentially connecting every sense organ with every muscle and gland cell, are provided by the cells of the nervous system.

We have seen how this originates, very early in our development, as a hollow tube along the back, made from a folding-in of the outer layer, the ectoderm. As this tube grows, its walls thicken considerably, and the central cavity becomes proportionately smaller and smaller, although even in the mature spinal cord and brain we can find vestiges of it. At intervals corresponding to the muscle segments, nerves grow out in pairs from the cord, lengthen toward the sides of the body, extend into organs, body muscles, limbs, or skin, branching as they go, until eventually every sense organ,

gland, and muscle is supplied with nervous connections. What are these "nerves"?

If we cut a nerve and examine it under high magnification, it appears to be made like a cable. It is a bundle of a great many fibers, most of them covered with a whitish insulating sheath of connective tissue, the whole bundle being held together by a similar sheath. These nerve fibers are sorted out, at the branchings of the nerve, to their separate destinations.

If we follow the course of these long fibers, we shall find that they are very long, fine extensions of the cytoplasm of nerve cells. Those which extend to a sense organ usually end in a brushlike tuft of little branches, while the ones which pass to muscle fibers end in a plate on the side of the muscle fiber.

The sensory nerve fibers grow out from cells which lie in little clumps, known as *ganglia*, alongside the spinal cord. Each fiber branches in or near the ganglion from which it arises; and if we follow the other fork, we can trace it into the dorsal side of the spinal cord, where it forks into several branches, most of which pass up toward the brain, but some of which grow down the spinal cord to lower levels. Some of these cells in man attain a length of more than five feet! Each branch ends in a tuft of microscopic branchlets which make contact with other nerve cells.

Other fibers in each nerve are motor nerve fibers, their impulses stimulating the muscle fibers to contract. These motor nerve fibers come all the way from cells in the spinal cord. The cells themselves are irregular, for they have numbers of short tuftlike projections (*dendrites*). Between the ends of the sensory and motor nerve cells in the spinal cord a third kind of nerve cell, known as an *association nerve cell*, makes connection. In this way an excitation of the sensory ending, by a pinprick on the finger, for example, will lead to transmission of an impulse along the sensory nerve fiber to the association nerve cell, and thence to the motor nerve cell, over whose fiber it will reach the muscle fiber, stimulat-

ing it to contract and withdraw the finger. This simplest type of hookup, in which the response is completely automatic, is known as a *reflex arc*. Never is nervous action as simple as this in reality—certainly not in the present example. The impulse from the sensory nerve cell will actually be passed to several association nerve cells, some, like the one

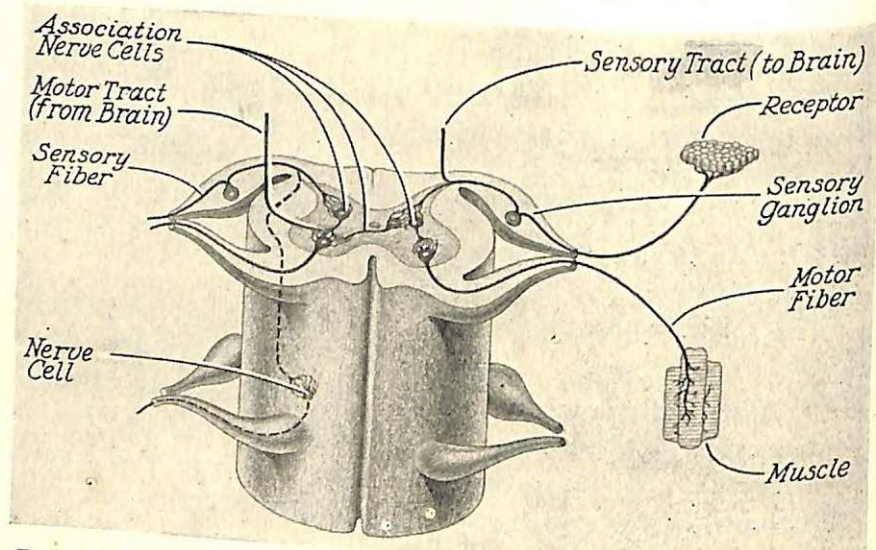


FIG. 100. Diagrammatic sketch of a segment of the human spinal cord, showing nervous pathways and connections. (Redrawn from Buchanan's *Elements of Biology*, after Kuhn. Courtesy of Harper & Brothers)

shown in Fig. 100, passing the impulse on to motor nerve cells, with the result that the response is a coordinated contraction of a number of muscle fibers; others passing the impulse on up the spinal cord to various parts of the brain, where numberless complications may be involved in our further responses, such as saying "Ouch," or kicking our tormentor, or plotting some deeper revenge.

The synapse

A very important feature of nervous transmission is the nature of the contact between the fibers of different nerve cells. This contact is known as a *synapse*.

A very significant thing about synapses is that, unlike nerve fibers, they *will transmit an impulse in only one direction*. Upon this characteristic depends the chainlike nature of the paths taken by impulses through the nervous system. Here is the basis for the perception of sequence within us—perhaps we are able to perceive time only because our nervous system is thus channelized. It is fascinating to speculate whether our boasted logic is an outgrowth of this—and we wonder vainly what the timeless existence of a *Hydra*, whose nerve net transmits in all directions, must be like.

In the second place, the synapse *appears to be improved by use in its capacity to transmit a nervous impulse*. Let us get a clear picture of all that this implies, for *it is very likely the basis of our ability to learn*. Through the nature of our hereditary pattern acting during development, we are provided with billions of nerve cells in spinal cord and brain, with a veritable wilderness of ready-made and potential connections. The ready-made ones provide us with a basis of unlearned behavior patterns which we call *reflexes* and, when more complex, *instincts*. It is true that man has very few of these ready-made behavior patterns in comparison with insects, for example, in which they predominate, for even our so-called “reflexes” are to a considerable extent developed by prenatal use and practice. Consequently, the mental wilderness is largely trackless, except as we make paths through it. Our first efforts to adjust ourselves are blind—excellent examples of *trial and error*. But somehow, whenever by mere chance a response is tried which turns out to be effective, the synapses along the pathway which lead to it are improved. As we accumulate experience, pathways are beaten down into “highways” along which nerve impulses are guided effortlessly, and we achieve a *habit*. This explains, too, why it is so hard to break a habit. It is as though nerve impulses, like men or cattle, resist being diverted from their accustomed route to one less easy.

The spinal cord

The spinal cord is the great trunk route for nerve fibers ascending to the brain or descending from it, besides providing numerous local connections. The cell bodies become arranged centrally, appearing in the form of a gray letter **H** in a cross section of the cord, with the white-coated ascending and descending fibers around the outside. Because the sensory nerve cells are outside the cord, in ganglia, the dorsal horns of the gray matter remain more slender than the ventral ones, which contain the large motor nerve cell bodies.

Most of the nerve fibers in the white matter cross over somewhere on their way up or down the spinal cord, and so the right side of the brain receives impulses from, and sends them to, the left side of the body, and vice versa. Nerve fibers of similar function occupy definite columns of the white matter, with the more local relays clustered mainly next to the central gray matter.

The forebrain

The brain, as we have seen, first shows up as a series of three bulging vesicles at the front end of the neural tube. As development proceeds (see Fig. 101), this original portion is so covered over and surrounded by new parts that it may be hard to discern, but it still forms the vital brain stem connecting all the major parts which have grown out from it.

In the sixth week of development the forebrain pushes forward two pouches, in front of the points of origin of the stalks which form the optic cups. These pouches grow forward, upward, outward, and finally backward, expanding until the brain stem is completely concealed by them. They are the two *cerebral hemispheres*, or *cerebrum*. Their enormous growth and development constitute the major difference between our brain and the brains of other vertebrates. In fish and reptiles they are small and are concerned entirely with the sense of *smell*. In reptiles a new area of growth occurs that becomes

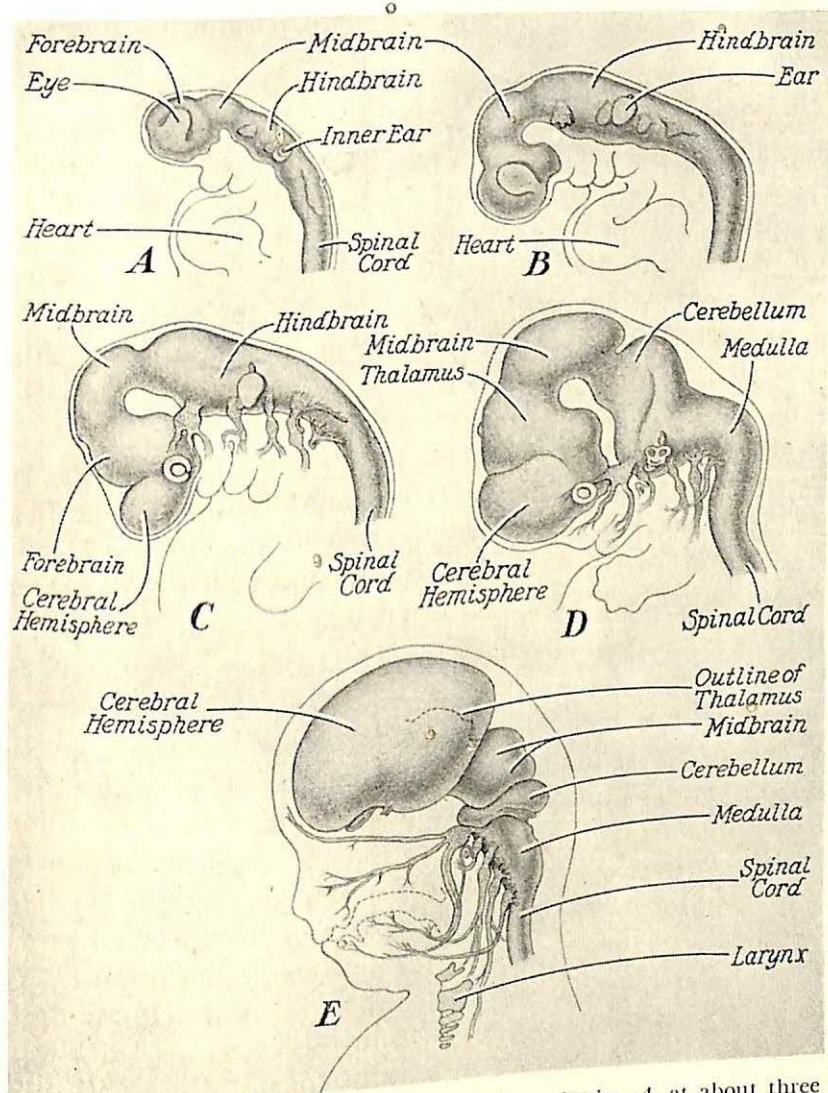


FIG. 101. Stages in the development of the human brain. A, at about three weeks. B, at nearly four weeks. C, at five weeks. D, at seven and one-half weeks. E, at three months. (Redrawn with modifications from Arey's *Developmental Anatomy*, after Patten. Courtesy of W. B. Saunders Company)

devoted to higher mental activities, such as the formation of associations and learning. It is this area which becomes progressively larger in birds and mammals, until it completely

overlies the original "smell-brain" and reaches its culmination in man.

The cerebral hemispheres have a layer of gray matter (nerve cells) on the surface, and the internal portion is composed of white matter. This reversal of the relative situations of gray and white matter in the spinal cord represents a new arrangement better suited to an enormous development of the gray matter. The surface area also becomes folded (only slightly in many lower mammals) into elaborate grooves and wrinkles in our own brain, thus supplying additional room for the nine billion nerve cells concerned with these newer activities of the brain. The functions of a number of the areas bounded by these grooves have been mapped. In the lobe just behind the ear lies the center for hearing and speech, at the rear is one for vision, and on either side of a prominent groove running from the top of each hemisphere down to the temples are parallel motor and sensory areas, from toes at the top to lips at the bottom. Other motor functions are to be found in the frontal lobes, but most of these and great areas of the posterior part cannot be assigned definitely. They are commonly thought to be the seat of the highest mental functions of all, for this is where we differ most from our closest relatives, the apes. These are known as *association areas*.

If we split the mature brain lengthwise (Fig. 102), a striking band of white matter at once catches our attention. It is the *corpus callosum*, a tract of nerve fibers which connects the two hemispheres. Just beneath this is a rounded body, the *thalamus*, connected by dense strands of fibers with the great internal reflex and distributing mass (*corpus striatum*) of each cerebral hemisphere. The thalamus is the final stage of the original forebrain, and is an extremely important region. All the ascending and descending fibers from the cerebral hemisphere pass through it; the automatic internal activities have here their ultimate coordination and control; it is the center of reflexes connected with smell and taste; pain,

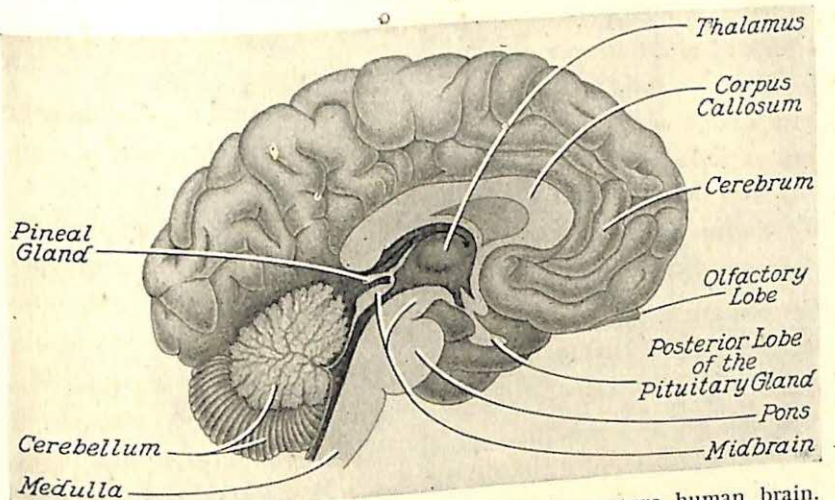


FIG. 102. Median longitudinal section through the mature human brain. (Redrawn with modifications from Plunkett's *Elements of Modern Biology*. Courtesy of Henry Holt and Company)

pleasure, and simple emotions are felt here; and temperature and the interplay of the endocrine glands are regulated in this region. Often, in considering the brain, the functions of the cerebral hemispheres alone are emphasized. We will do well not to forget that below these lies the brain stem, inconspicuous but essential. As C. J. Herrick says, "Whenever elementary emotions . . . are complicated by interpretations, are elaborated through association with other kinds of experience into sentiments, sympathies, aversions, jealousies, and the like, or are deliberately joined with impulse in voluntary action, then thalamus and cortex are working in partnership. The thalamus supplies the emotional coloring, the agreeable or disagreeable quality, and the simple impulsive drives; the cortex supplies the intelligent guidance and rational control. The thalamus, then, discharges two ways, downward toward the motor centers and upward toward the cerebral cortex. The former regulates and reinforces our elementary visceral reactions and is one of the most primitive functions of the brain. The latter links these reactions and

the accompanying emotions with the higher centers of intelligent control and keeps them in hand in the more restrained life demanded by good society." ¹⁰ The thalamus thus provides a goodly share of the behavior patterns that make up our personality!

The midbrain

This part of the brain stem, which in fishes is the most prominent region, remains relatively undeveloped in human beings. There are four little hillocks just behind the thalamus, and a floor through which the ascending and descending nerve fibers pass from thalamus to hindbrain. Yet there is something very interesting about these four hillocks, for to the first pair are distributed nerve fibers from the eyes, which have crossed and entered the brain below the thalamus, just in front.

The nerve fibers from the left and right sides of each eye are sorted out together at this crossing, so that the two images of each object, seen by each eye from a slightly different angle, are made to coincide through distribution to the same part of the brain. In this way we acquire stereoscopic vision and a finer judgment of distance, a gift only the monkeys and apes share with us. These first two little hillocks of the midbrain, to which some of the optic nerve fibers pass, still remain our center for visual reflexes, and this whole part of the brain in lower vertebrates is concerned with vision.

The second pair of little hillocks is a similar center for hearing reflexes, such as "pricking up the ears." How is it that we, who depend heavily upon sight and hearing as our avenues of information, boast the greatest development ever attained by that part of the brain originally concerned with smell, and have such insignificant "sight-" and "hearing-brains"? Those genes which, by mutation in our ancestors, led to the progressive development of our cerebral

¹⁰ *The Thinking Machine*, ed. 2, p. 118. University of Chicago Press, 1932.

hemispheres must have been superimposed on the hereditary pattern of a mammal that, like most other mammals today, depended primarily on his sense of smell and had a relatively large "smell-brain."

With an increased predominance of the sense of smell, those centers in the forebrain which correlate smell with visual, auditory, and other sensations, and with motor activities, became tremendously developed. In short, practically the entire interpretation of these sensations and the voluntary control of the muscles and glands was transferred to the various areas of the cerebrum, leaving only reflex control in the original centers. Many of the sensory fibers from the eyes and ears were even "short-circuited" to the correlating centers of the cerebrum, so that now we "see" and "hear" in these centers rather than in the midbrain.

The hindbrain

The hindbrain comprises three main structures. Two, the *pons* and *medulla*, constitute the hind portion of the brain stem, which consists in large part of nerve fibers which continue on into the spinal cord and in the other direction pass to midbrain, thalamus, and cerebral hemispheres. Many of these, too, terminate in this region, for from it emerge all of the twelve pairs of cranial nerves except the first four. (Two of these first four, the olfactory and optic "nerves," are purely sensory—smell and vision—projections of the forebrain; the third and fourth are motor, controlling some of the muscles that move the eyeball.) The eight pairs of nerves of the hindbrain include motor nerve fibers for the eyeball, jaw and face, pharynx, tongue, salivary and tear glands, neck, and even such lower organs as trachea, esophagus, stomach and small intestine, liver and pancreas, and diaphragm and heart; they also include sensory nerve fibers from most of these parts and, in addition, the very important auditory nerves from the ears. Such a number of important nerves evidently re-

quire numerous associations in the part of the brain they enter; consequently the pons and medulla are great reflex and relay centers. Here the rate of respiration and of heartbeat, and the determination of the amount of blood flow to particular parts of the body, swallowing, vomiting, coughing, and sneezing are all regulated.

The *cerebellum* grows out from the roof of the hindbrain close to the midbrain. Like the cerebrum, the cerebellum has its cells (gray matter) on the outside, with the nerve fibers forming a white treelike structure in the interior. Fibers connecting its right and left lobes with the cerebrum cross underneath the brain stem, forming the conspicuous ventral part of the pons.

The sensory nerve fibers from the part of the ear which is concerned with balance, position, and movement in space enter the pons and are relayed to the cerebellum, which is the great reflex center for muscle coordination. Practically all the voluntary muscles are involved in maintaining our equilibrium, and this part of the brain therefore becomes a center for their coordination even in voluntary movements, although the original impulses may come from the cerebral hemispheres.

The autonomic system

We have thus far overlooked one very important part of our nervous mechanism. There are two additional chains of ganglia, a pair to each body segment, which parallel the spinal cord. These are the *sympathetic trunks* of the autonomic system. Apparently they are formed by the migration of individual cells from the neural crest, a strip of ectodermal cells left along the back, between the outer ectoderm and the neural tube, when the latter is closed over. They journey down the dorsal (sensory) nerve roots, some of them stopping on the way to form the spinal ganglia. Other cells migrate out from the spinal cord along the ventral (motor) nerve roots. When the migratory cells reach the correct spots (we

may well wonder how they recognize them), they form clusters and send out nerve fibers to connect with adjacent ganglia until the chains are formed. They also send out nerve fibers to the internal organs, governing their automatic activities. Our solar plexus is a cluster of nerve fibers and ganglia belonging to this system, and we have all experienced how a blow over it "knocks the breath out of us" by paralyzing, among other things, the nerve supply to the diaphragm.

The terminal nerve cells of the sympathetic ganglia liberate *sympathin*. This is a substance which has a powerful stimulating effect upon the organs innervated. But a regulation limited to stimulation and nothing else would be most ineffective. The control of the autonomic system over the internal organs is based on antagonistic action. Besides the sympathetic portion, there is a *parasympathetic* portion that innervates the majority of the same internal organs. The terminal nerve cells of the parasympathetic ganglia liberate *acetylcholine*, a substance which strongly inhibits the activities of the organs innervated. The sympathetic portion of the autonomic system is connected with the spinal nerves of the thoracic and lumbar regions; the parasympathetic trunks arise partly from the hindbrain and partly from the sacral region of the spinal cord.

The autonomic system is connected also with the central nervous system by sensory nerve fibers. In every segment these pass through the autonomic ganglia to the spinal cord by way of the spinal nerves. Accordingly, the internal organs are not completely isolated from our brains. Sensations of pain may rise from them into our consciousness, and some measure of control can be exerted over the organs by the medulla and the thalamus. Yet fortunately for us, because of their largely reflex system of control, we can go along happily oblivious of our inner workings most of the time, free from the necessity of attending to them consciously.

CHEMICAL CORRELATION

Besides the nervous system, other means of correlating the varied activities of the different parts of our complex bodies are also provided—chemical means, resembling in their action the “organizers” of earlier development. Substances synthesized in one place pass into the blood, are distributed through our whole system, and here and there exert some effect upon an organ especially sensitive to them. These substances are the *hormones*, and the organs which produce them are called the *endocrine*, or ductless, *glands*. They are widely scattered in our bodies.

We have already noticed how the intestine produces secretin, which sets pancreas and liver to secreting pancreatic juice and bile whenever food enters the intestine from the stomach. Another hormone, very similar chemically to secretin, is produced in the same region, and stimulates the gall bladder to contract and discharge the bile stored in it into the intestine. And, during our survey of the digestive system, we have seen how the islet tissue of the pancreas produces insulin.

The *parathyroids*, products of the third and fourth pairs of gill pouches, are other endocrine glands of vital importance to us. They regulate the concentration of calcium ions in our blood, upon which there depend not only the strength and firmness of our bones and the efficiency of our calcium metabolism but also the irritability of our muscles. Since these tiny glands come to lie on the very surface of the thyroid gland, and may even be imbedded in it, an operation on the latter for goiter, unless performed with modern precautions, may inadvertently cause the removal of the parathyroids too. Then the calcium concentration of the blood *falls alarmingly, the muscles and nerves become more irritable*, the muscles begin to twitch, and finally go into con-

vulsive spasms which end fatally, unless a calcium salt or a dose of the hormone is injected into the blood. When a tumor of the parathyroids results in excess secretion of their hormone, calcium is lost from the bones to the blood, the skeleton loses strength, the teeth decay. *Thus the parathyroid hormone controls, on the one hand, muscle and nerve irritability and, on the other hand, the adequate development of bones and teeth.*

The thyroid gland

The hormone of the thyroid gland, thyroxin,¹¹ is a relatively simple organic chemical substance, an amino acid containing *iodine*. Only very slight amounts are necessary at any one time—in fact, the amount normally produced by one individual in a whole year ($3\frac{1}{2}$ grains) could be put into three or four medium-sized gelatin capsules. Yet a deficiency of thyroxin during the years of childhood and adolescence is sufficient to make one an imbecile, of a type known as a *cretin*. These unfortunates are stunted and deformed in body as well as in mind, all for the lack of a tiny bit of a certain chemical substance, which, if supplied soon enough, can do wonders in restoring to them a relatively normal mind and body. What role has thyroxin in our body activities that makes it so important?

The effects of an excess or an insufficiency of it reveal the answer. The person with too active a thyroid gland has a faster heartbeat and higher temperature than normal. He frequently is excitable and irritable, oversensitive and hard to get along with. He may suffer from insomnia, and is likely to be thin. Finally, if the overactivity of the gland is due to its enlarged size, there will be a goiter on the throat, along with popeyes. What a contrast in the person who has an underactivity of the gland! The action of muscles, glands, and circulation is sluggish; body temperature is lower, and

¹¹ *The actual hormone is probably a compound of thyroxin with a protein.*

hands and feet are often cold; there is a tendency to put on fat, and the skin is often puffy. The personality, too, suffers, for such a one is inclined to be indolent and slow of wit. In other words, *thyroxin regulates the rate of metabolism*, which is all-pervading in its influence.

Another type of goiter results from an effort to compensate for a lack of iodine in the diet by an enlargement of the thyroid gland. Naturally, this kind of goiter occurs mainly in certain regions where iodine is scarce. This is principally in glaciated regions where the action of the ice has removed the topsoil containing most of the iodine. Switzerland and our own Great Lakes region are examples of "goiter belts," where in places one fourth of the men and more than one half of the women are affected. Use of iodized salt can cut this incidence down to nearly zero; for example, among Detroit school children it was cut from 35 per cent to 1 per cent in eleven years. These goiters develop especially at periods when the body activities are highest and the demand for thyroxin is accordingly greatest, as before birth, at puberty, and during pregnancy and nursing.

The thymus gland

Developing from the hinder parts of the third and fourth gill pouches is a huge gland—the thymus—that is still largely a mystery. It is large at birth, begins dwindling in infancy, and has usually disappeared completely by puberty. Has it something to do with growth, with the attainment of sexual maturity, or with the growth of the skeleton and the utilization of calcium? All these are claimed, but none of them is known with certainty. At present our chief interest in this gland is that its huge size in newborn babies may prevent easy breathing, and even suffocate them by pressing on the windpipe. Often nowadays babies are x-rayed to see whether there is any danger of this, and then, if necessary, are given an x-ray treatment that reduces the size of the gland.

The adrenal glands

Each of these glands, situated like yellowish caps on the top of each kidney, is really two glands, for the inner and outer portions have different origins and synthesize entirely different hormones. The medulla, or central portion, produces *adrenalin*. Its chemical structure has been worked out, and it can be synthesized in the laboratory as successfully as in the adrenal glands in the body. It is wonderfully potent, minute injections speeding up the heartbeat, raising the blood pressure, diverting blood from the skin and internal organs to the muscles, at the same time increasing the sugar concentration of the blood, raising the resistance to fatigue, and speeding up blood clotting. In all of these effects it duplicates the action of the sympathetic portion of the autonomic nervous system, a fact of great interest because the medulla of the adrenal glands develops in the embryo from special cells migrating out of the solar plexus of the sympathetic system, and the terminal nerve cells of the sympathetic produce *sympathin*, which acts like *adrenalin*.

The effects of *adrenalin* are those associated with excitement, anger, fear, and danger, and should be of great help in emergencies. Many physiologists believe that *adrenalin* plays such a role, but there is still some doubt whether it actually is secreted in extra amount during crises. As to its normal role, it has not been conclusively shown to have any. It is present in the blood in only one part in 20,000,000, and this is too dilute to have any obvious effect. At least removal or inhibition of the medullas of the adrenals has no clear-cut effect. Read the opinion of textbooks on this point with caution, even though it is hard to think of such large and active glands and of so potent a hormone as valueless to us.

The outer portion of the adrenal glands, their cortex, grows from the mesoderm. It produces a hormone or several as yet unseparated hormones called *cortin*. This is unquestionably vital, removal of the entire adrenal glands being

quickly fatal. Cortin is perhaps the means of controlling the concentration of the sodium, chloride, and potassium ions in the blood, as disease of the adrenalin cortex results in lowering the two former and raising the latter. The secretion of the adrenal cortex also has marked effects upon sexual development, as will be seen later.

The pituitary

In a little hollow in the floor of the cranium, just beneath the midbrain, lies the pituitary body, a gland about the size of a hazelnut. Its two parts, anterior and posterior, are of separate origins, and, like the two parts of the adrenals, may be considered essentially different glands.

Most of the posterior part is a growth from the lower part of the thalamus, with which it remains connected by a stalk. Substances have been extracted from it which powerfully stimulate smooth muscles, especially those of the smaller arteries and of the uterus, to contract. This raises the blood pressure, steps up the secretion of urine, and causes spasms in the uterus, even in a concentration of one part in 15,000,000,000 of blood, so that the extract is a potent drug in the hands of a doctor for speeding up delivery at childbirth. However, whether or not it is normally secreted at such times is uncertain, and we must hesitate to label it definitely as a hormone, since removal of this lobe of the pituitary seems to have no effect upon blood pressure or labor.

The *anterior lobe of the pituitary* is a portion of the original pouch from the roof of the mouth (see p. 277). No less than five hormones are known to be produced here. One of them *regulates the growth of the body*. Should the gland become overactive in producing this hormone, a phenomenal increase in size will take place. Most of us are familiar with circus giants, and have seen news pictures of an eight-foot, 400-pound boy, or of a huge one-time heavyweight boxing champion of the world. In 1935 there were reports

of a young Egyptian carpenter who fell off a ladder on his head, suffered a derangement of his pituitary secretion and grew ten inches that year and eight the next! These giants nearly all suffer from circulatory difficulties—the heart is strained trying to pump blood around so huge a frame. If the hyperactivity of the gland sets in after the growth zones of the bones are already ossified, then, instead of gigantism, growth is mainly confined to an enlargement of hands, feet, and face (*acromegaly*). Often this condition, in which the skin also tends to be too big for the body and to hang in great loose folds, and gigantism of some degree are associated. This is strikingly exemplified in certain breeds of dogs, such as the St. Bernard or the mastiff, with their huge jowls. This as the racial character of pituitary activity shows that it is genetically influenced to a considerable extent, both as to degree and time of onset. Human pedigrees indicate that the factors for tallness are multiple and mostly recessive. It is unlikely that all of them act through the pituitary.

Conversely, underproduction of the pituitary growth hormone during development results in midget size, as in the familiar human hereditary type, or in bantam chickens. This is purely a dwarfing of skeletal size. There is a normal variation of intelligence in these types. In animals, growth can be restored to normal if implants of active anterior pituitary tissue are made before the bones are "set," their growth zones ossified; but attempts to help human dwarfs by this means have not been entirely successful so far. The time of onset of the deficiency will clearly be very important here, just as in the case of hyperactivity. When the deficiency sets in after the trunk skeleton is completed, but while the limbs are lengthening, the result is deformity rather than a miniature; for the trunk and head are then of normal size, but the arms and legs are curtailed. This produces the "court jester" type of dwarf, the Pekingese dog, and similar types. This condition is usually recessive in inheritance, while brachydactyly

(short fingers), still later in onset and consequently much less deforming, is a dominant. These genetic types afford a good example of the way in which genes may produce their several effects by determining the relative times of the onset and duration of processes, just as in previous cases we have seen how they acted upon the relative rates of processes.

It is evident that this hormone must be different from that of the thyroid, a deficiency of which during development also produces dwarfism, but with stunting of the intelligence. Thyroxin cannot replace a deficiency of the pituitary growth hormone. On the other hand, *normal activity of the anterior pituitary is requisite for the development and normal function of the thyroid, the parathyroids, the adrenal cortex, the ovaries or testes, and other glands.* It is the kingpin of the whole endocrine system. Its control over the thyroid is by a separate hormone; its regulation of the adrenal cortex probably by still another. There is growing evidence that it regulates the insulin production of the pancreas, and the metabolism of fats. Whether or not its control over the parathyroids is by a hormone other than the growth hormone, is still rather uncertain.

The three remaining hormones of the anterior pituitary are all associated with the development and functioning of the reproductive system, and can be better understood as we outline the development of this system.

PROVISION FOR THE FUTURE OF THE RACE—REPRODUCTION

Our sex is determined, as we have already seen, at the very instant we are conceived. If the sperm contributing our paternal heritage carries an X-chromosome, we become female; if it carries the smaller, gene-empty Y-chromosome, we become male. In spite of this genetic determination of our sex, however, we are more than six weeks on the road to birth before there is any further sign of sexual distinction.

The gonads (ovaries or testes)

It is not that development of the sex organs has not commenced. They are well along, *but so far completely alike in both sexes*. Both *ovaries* (female) and *testes* (male) begin as projecting folds of the mesoderm just below the developing kidney ridges in the body cavity on each side of the intestine

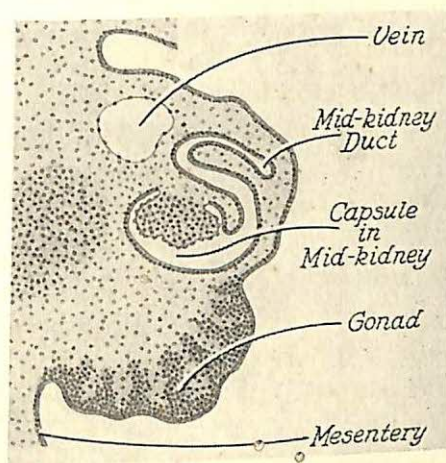


FIG. 103. Origin of the gonad. A cross section of the kidney and genital ridges from a five- to six-weeks-old human embryo. (Redrawn with modifications from Arey's *Developmental Anatomy*. Courtesy of W. B. Saunders Company)

(Fig. 103). The sex organs lengthen and round up. They separate from the kidneys, and, like the other organs, hang suspended from the dorsal side of the body cavity, in slings (mesenteries) of the membrane which lines it.

Within the sex organs, at about two months after conception, *sexual differences* appear. In *males*, cells within the testes become grouped into *cords*. These become hollow, making the testis tubules in which the *sperms* eventually arise. Each tubule has a sheath of connective tissue cells. Next to this are the prospective sex cells, which are not transformed into sperms until puberty.

In *females*, no definite cords of cells form in the ovary, as they do in other animals or in males. Instead, the whole central mass of cells becomes recognizable as a group of prospective egg cells. Connective tissue invades these and breaks them up into small clusters. Most, or even all, of the prospective egg cells then degenerate, except those closest to the outside. Others arise from the germinal layer of cells covering the ovary. In the last few months before birth each egg becomes surrounded by a *follicle*, or capsule of nurse cells. As in the case of the sperms, the growth and meiosis of these prospective eggs are delayed until puberty. Shortly after birth the formation of additional egg cells stops. There is even, according to one investigator, a degeneration of great numbers. He estimated that at three years of age there are approximately 400,000, and that five years later this number has been reduced to about 40,000, while at puberty there are even less.

The sexual ducts

The tubes or ducts through which sperms and eggs make their exit from the body are not growths from the ovaries or testes themselves. *The male ducts*, if not the female, are *derived from the remains of the mid-kidney*.

The main mid-kidney ducts, one on each side of the body, open into that allantoic portion of the cloaca which becomes the urethra, below the urinary bladder (see Fig. 87). Parallel, budding from a groove in the mesoderm covering each mid-kidney, a second pair of ducts develops, flaring into trumpet-like mouths at the head end. (In sharks these ducts arise by partitioning the main mid-kidney ducts, splitting them in two. This has led many embryologists to believe that this second pair of ducts traces back genetically to the mid-kidney ducts, and that its present origin in our bodies represents one of the developmental short cuts frequently to be found.) This second pair of ducts furnishes the rudiments for the female sexual ducts, while the original mid-kidney

ducts become the sperm ducts. *Whatever our sex, we thus start out in life equipped with both male and female sexual ducts.*

The external genitalia

During the sixth week of our growth (Fig. 104*A*), a rounded hump appears just in front of the good-sized tail. On its sur-

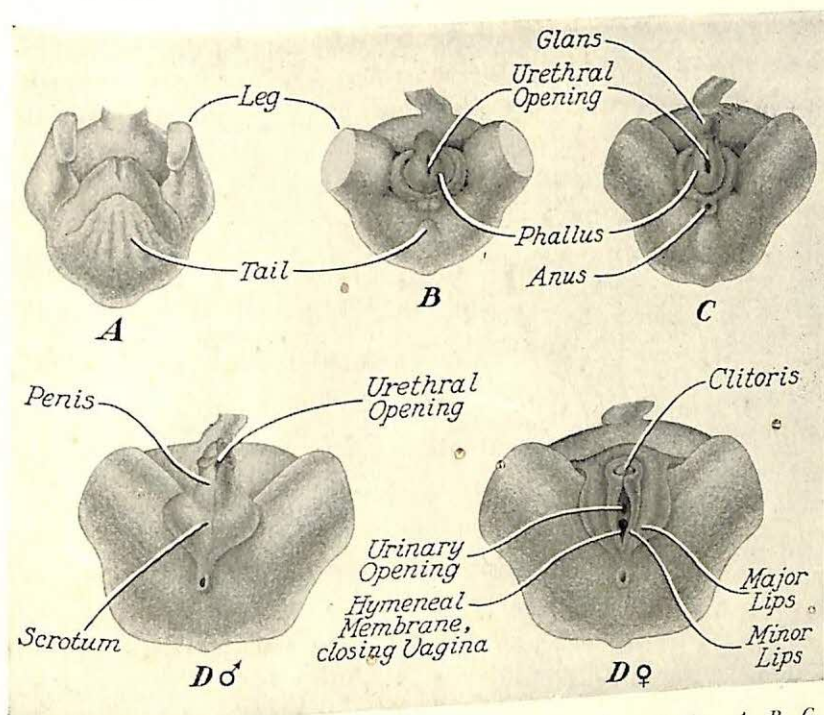


FIG. 104. The embryonic development of the external genitalia. *A, B, C*, early, middle, and late stages in the indifferent period. *D*, male and female external genitalia after differentiation is well along. (Redrawn with modifications from Parshley's *The Science of Human Reproduction*. Courtesy of W. W. Norton & Company)

face, next to the tail, is a shallow groove, the floor of which is a thin membrane closing the urethra. (The anus just below this is also still closed by a membrane at this time.)

A week later (Fig. 104*B*), the hump has lengthened into a

cylindrical *phallus*, with a rounded cap-like end known as the *glans*. At the base of the phallus are rounded swellings. The membrane closing off the urethra ruptures at about this time. (The tail has by now dwindled to a nubbin.)

At eight weeks (Fig. 104C), the genitalia are just beginning to appear different in male and female. The urethral opening is now shorter, and in the male the portion which remains is farther out on the phallus than in the female. Meanwhile the phallus has grown considerably, and the glans is set off by a neck.

Male and female

What starts the differentiation of the ovaries and testes? This depends upon the chromosomal constitution, the primary effect of which is not known, but may possibly be to fix the basal rate of metabolism at a higher level in males than in females, for this is an early and fundamental difference between the sexes.

We should remember that the gonads are basically so similar that an ovary may, under abnormal conditions, develop into a testis, producing one of those extremely rare unfortunates, the human hermaphrodites, who have one ovary and one testis. Or, occasionally, disease may result in the destruction of a whole ovary or a part, whereupon it may be replaced by a testis. Well known is the instance of the Scottish hen who stopped laying eggs, metamorphosed into a rooster, and became the father of two chicks. Her one functional ovary—it is characteristic of female birds to have only one functional sex organ—had been destroyed by tuberculosis, and the other rudimentary sex organ had then developed into a testis.

As the sex organs diverge developmentally they begin to function as endocrine glands, testes somewhat earlier than ovaries. The interstitial cells between the tubules of the testis produce the male sex hormone (*testosterone*), while the female sex hormone (*theelin*, or *estrin*), which accumulates in the fluid

filling the follicles, has a source not specifically clear. These two hormones are very similar in chemical structure—they are both sterids—and the switch between them must be rather easy. In fact, both hormones appear to be produced in each sex even in adults, and the course of development, as was emphasized earlier (in Chapter IV), is determined by whichever one predominates. The further development of the sexual ducts and genitalia (see Fig. 104) is influenced by whichever sex hormone is present.

Male

SEXUAL DUCTS

Half a dozen or so of the mid-kidney tubules closest to each testis grow into it and make connections with the testis tubules. Lengthening considerably, these mid-kidney tubules and the upper portion of the main duct into which they open all lie coiled on the testis, forming the *epididymis*, a storage place for sperms.

The female pair of ducts completely degenerates, except for a tiny bit of the merged portion just at the bottom, and another, clinging to each testis, at the top.

Female

The mid-kidney tubules and ducts degenerate leaving only vestiges.

The funnel-shaped mouths of the female ducts (oviducts) fit over the ovary, ready to pick up any mature eggs released. The lower ends merge and thus give rise to the *uterus* and *vagina*. These, at first indistinguishably alike, become clothed with involuntary muscle, especially abundant about the upper portion, which becomes the uterus. The vagina, which at first opens into the urethra, is prolonged by a partition that grows down until vagina and urethra are completely walled off and open separately.

EXTERNAL GENITALIA

The phallus continues to lengthen until it becomes a *penis*. The opening on its underside is closed up and a new one appears at the tip. The two swellings on either side of

The phallus remains short, consisting mainly of the glans portion, and is called the *clitoris*. The swellings on either side remain undeveloped, as compared to the male, and make

Male

the base of the phallus enlarge into a sack, the *scrotum*, and the testes descend into this assisted by the contraction of a ligament fastening them to the bottom of the scrotum.

Female

the *major lips*, while the margins of the urethral groove form a pair of inner, *minor lips*. At the opening of the vagina there is formed a perforated membrane, the *hymeneal membrane*.

The quiescent period

Sexual development is suspended from birth through childhood. Production of the hormones from testes or ovaries dies down. This is apparently due to the control exerted by the hormone from the adrenal cortex, which in its turn is controlled from the pituitary gland. It seems likely that the fairly frequent human "pseudohermaphrodites," who have ovaries but male external genitalia, result from an abnormal activity of the adrenal cortex before birth, as the hormone cortin is known to exert a strong impulse toward the development of male structures. At any rate, it is clear that abnormal activity of the adrenal cortex during childhood may cause puberty to set in early. In boys this leads to remarkably early growth and maturity, both sexual and mental, so that even when one year old they may enter puberty, and by the age of five be ready to die as old men. Girls mature in a similar way, but with an added superimposition of male characteristics, such as a growth of beard and transformation of the external genitalia to the male type.

This can hardly be the whole reason why sexual development is suspended in childhood. Other glands and their products may be involved; but we can hardly doubt that the adrenal hormone, cortin, helps to control the situation.

Puberty

At about fifteen years of age in boys, and a year or so earlier in girls—these ages are for our temperate clime; in warmer regions puberty sets in a couple of years earlier—the ovaries

or testes resume production of the sex hormones. This brings to maturity the reproductive system, last of all the organ systems to reach its functional level. Many parts of the body are affected. The larynx enlarges and the vocal cords lengthen, so that the voice becomes deeper, especially in males. Hair grows in the armpits and around the external genitalia, and boys commence to sprout a beard.

The major changes in males are naturally internal, within the testes themselves. Here the prospective sperm cells begin to divide rapidly, then to grow, pass through the two meiotic divisions, and transform into sperms. As they go through these successive steps, they are pushed into the central cavity of each tubule by the newer cells being formed by mitosis beneath them. Once the sperms are mature, they pass, still beneath them, into their storage chamber, the long coiled epididymis. The prostate gland, seminal vesicles, and other glands which lie around the sperm ducts, also become functional now, secreting a milky, odorous, alkaline fluid which vitalizes the sperms into activity when they come in contact with it. The mixture of fluid and sperms is known as semen.

In girls the breasts enlarge, and the pelvis broadens so that its aperture is larger. These are vital preparations, as the fetus must pass through this bony ring at childbirth and must be nourished afterward. The broadening of the pelvis throws the hip joints out to the sides. Consequently the thighs slope in toward each other, and, to preserve the balance, the knees become angled instead of straight! (Similar but slighter alterations occur in the shoulder girdle and at the elbow.) These changes produce the typical female figure with its flowing curves, and result in the slight physical awkwardness which handicaps most women in competing with male athletes.

The internal changes are more important. The ovaries mature, and the early follicles, which have heretofore degenerated after reaching a certain stage, enlarge one by one. As each prospective egg finishes storing up its food sup-

ply, it passes through the first division of meiosis, forming one minute "polar body." The follicle by now projects from the ovary as a sphere about the size of a small marble. It then opens, and the egg is released, along with its surrounding fluid, to be caught up by the mouth of the oviduct! Here it awaits fertilization, which must come within two or three days at most, as after that time degeneration will set in.

Meanwhile changes have been going on in the uterus under the influence of the increased production of theelin by the ovary. The lining of the uterus becomes more glandular and more richly supplied with blood vessels day by day, and by rapid cell division becomes greatly increased in thickness. But the preparation for the reception of the fertilized egg is not yet complete. In the now empty follicle of the ovary there forms a clump of yellow cells (*corpus luteum*) that begin to produce a second ovarian hormone, *progesterin*. Under the influence of this hormone the glandular lining of the uterus commences to secrete a sticky fluid, which is necessary for the implantation of the fertilized egg in the uterus, and perhaps nourishes it before the blood connections are provided by the growth of the placenta.

If the egg is not fertilized, the production of theelin by the ovary declines, the corpus luteum begins to degenerate, and then the whole superficial lining of the uterus sloughs off. This, accompanied by a loss of blood from the rupture of the rich supply of blood vessels in the lining, is *menstruation*, generally the first startling sign to a girl that she is approaching maturity. As the ripening of the follicles is limited to recurrences roughly once each lunar month (twenty-eight days), the menstrual cycle, with its frequent accompaniment of ill-ease during menstruation, sets in.

Menstruation and *ovulation* (the release of the egg from the ripened follicle) are thus alternating phases of the cycle, the latter coming about nine or ten days after menstruation stops. (This varies individually from the twelfth to the twenty-first day after the onset of menstruation.) What regu-

lates the cycle with such exactitude? What is responsible, in other words, for the rhythmic increase and decrease in the production of theelin by the ovary? At least a partial answer to these important questions has been found in the action of a hormone of the anterior pituitary. This also varies in a cyclic way, apparently because the theelin itself, as it increases in concentration, inhibits its production (Fig. 105).

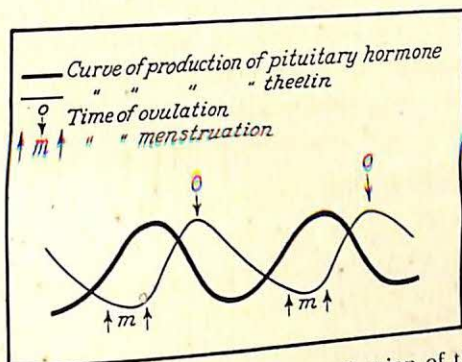


FIG. 105. Curves to show the relation of the production of the hormone from the anterior pituitary gland to that of the hormone from the ovarian follicles (theelin), and the consequent regulation of the cycle of menstruation and ovulation, as explained in the text.

The growth of the corpus luteum is also stimulated by a hormone from the anterior pituitary, one which is produced during the intervals when the theelin-stimulating hormone is inhibited.

Mating

The impulse to seek a mate, the sex urge, comes from the presence of either male or female sex hormones in the blood. Females among the lower mammals, however, are receptive only at the height of theelin secretion. They come periodically into "heat," as for example, twice a year in dogs, every three weeks in cows, every week in mice. As this is the period of ovulation, here evidently is nature's method of insuring pregnancy. But note the effect on the male! He is usually interested in a female only while she is in "heat"; as soon as

she has passed the period, he is off to another. The "family," in our sense, does not exist among the lower mammals. Either the female rears her cubs alone, or some powerful bull gathers a whole harem of females about him, keeping them his by furiously fighting off all younger upstarts. In our species, however, this physiological limitation of receptiveness on the part of females to certain periods has disappeared, and the human monogamous family became possible.

The act of mating (*coitus*) is itself one of nature's great economies, insuring the highest percentage of fertilization and pregnancy. The pleasurable erotic sensations, widely diffused over the body, but centered in the stimulation of the glans of penis or clitoris, contribute toward insuring reproduction. In the act of mating, a vast quantity of sperms—several hundreds of millions—are expelled from the epididymis, and mixed with the secretions from the prostate and other glands, which render them active. The semen is then deposited by the erected penis in the female vagina. (Both penis and clitoris contain spongy bodies which stiffen by means of an influx of blood under sexual excitement.) The sperms then swim by their own efforts up through the uterus and along the female sexual ducts until they encounter the egg. This direct transmission of sperms from the male to the female is a far more effective way of insuring fertilization than the method employed by fishes and frogs, whose eggs are first laid in the water and then have the sperms poured out near them. In land animals, consequently, fewer eggs need be produced, since there is little waste from lack of fertilization; and, as the egg carries considerable stores of food, this is an important saving.

A second and perhaps more important relation is that fertilization of the egg before it passes down the oviduct enables it to be covered with additional layers of food and with a protective shell before it is laid. This would appear to be of little importance in mammals, but mammals have

evolved from reptiles, to whom this ability must have been of primary importance in their conquest of the land.

Pregnancy

The story of the descent of the fertilized egg to the uterus, and of its implantation and development there, has already been told. Here we are concerned with the mother's part. The most important warning of pregnancy is the omission of menstruation. Why does upset of the regular cycle occur?

Somehow the implanted embryo stimulates the corpus luteum to keep on growing, and this, if we can reason from what is true in rabbits, dogs, and guinea pigs, is necessary to prevent an abortion. Under the influence of the progesterin, the lining of the uterus, instead of sloughing off, continues to thicken and prepares to take part in the formation of the placenta. After about three weeks, though the corpus luteum continues to grow, it is no longer essential; from the time when the placenta is developed, menstruation is apparently checked by the production of theelin there.

Slowly the production of theelin rises, until late in pregnancy there is considerably more of it in the blood than at times of ovulation in the regular cycle. The anterior pituitary hormone is thought to be responsible for this. It increases in amount up to the fifth month, and then declines. The cycle rather resembles a regular menstrual cycle stretched out to ten times its usual length (Fig. 106).

These two hormones are so abundant in pregnant women that considerable quantities are present in their urine. In fact, such urine furnishes an important source of supply of theelin for medical and experimental use. Moreover, by injecting the urine into female rabbits or other test animals, an accurate test for pregnancy has been found even in the first month.

The anterior pituitary steps up its production of the growth hormone, and the thyroid and adrenal cortex, too,

become more active. These conditions seem to be for the benefit of the embryo. The strain on all the endocrine glands at this time is severe, and may lead to upsets and disturbances. *Supplies of iodine, calcium, insulin, and the vitamins must be kept adequate.* "Pregnancy," says Hoskins, "is a condition exquisitely dependent upon endocrine factors."

The mounting tide of theelin sets up a renewed development of the breasts. Then, toward the end of pregnancy, the anterior pituitary commences to supply another hormone,

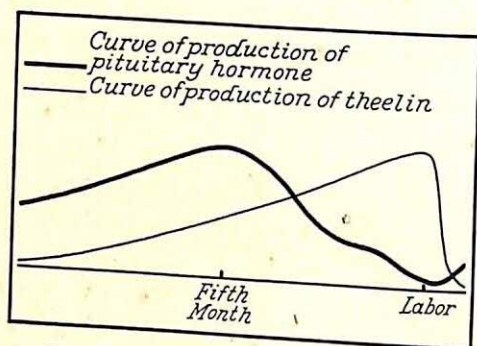


FIG. 106. Curves to show the relation of the production of anterior pituitary hormone to the production of theelin during pregnancy.

prolactin, which stimulates the mammary glands to prepare for the active secretion of milk. So potent is it that it will evoke milk production even in male rabbits and guinea pigs if their breasts are first stimulated to develop by injections of theelin and progesterin.

At last, labor and childbirth! Then once again is resumed the cycle of ovulation and menstruation. One further point we should like to know. Why is it that only one egg is normally permitted to mature at a time, while in some lower animals litters of more than a dozen are produced? Obviously, the human uterus is not really adequate to accommodate a large number of embryos, as is that of mammals like mice or rabbits, in which the embryos develop in the "horns" of the uterus (that is, in the lower portions of oviducts). It

is clear, too, that the tendency to have twins or other multiple births runs in families. Primates—monkeys, apes, and man—like some other groups, must have acquired genes that, in line with the extended term of pregnancy, limit the number of eggs maturing at one time, and so cut down multiple births. But how these genes act—through what endocrine hookup or otherwise—we have not yet discovered.

We have now completed the great cycle of a human generation, from conception to contributing to conception, from birth to giving birth. This is the story of the continuity of life through genes and protoplasm, and of its unfolding as genes interact with their environment. Now seeming direct and foresighted, now circuitous and wasteful, this early development of ours is the basis of our later capabilities and handicaps, similarities and differences, needs and problems. By learning its conditions, we may be enabled to lay the best possible foundations.

Yet our responsibility is broader than the immediate one of reproducing our kind. The longer our young remain immature and dependent, the longer will we adults be concerned with their care, and our biological responsibility be protracted. Here social and economic factors necessarily begin to concern us. In the world of today life is becoming so complex and so dangerous that ever greater parental care is called for, ever longer training is required to make our children self-sufficient. The generations are stretching out. Man as an animal might mate on the average at sixteen or eighteen years of age; as a social creature he is mating at twenty-five—perhaps, in a few more years, at thirty. The biological changes in the middle-aged and the old are becoming more and more important. What do we know about them? To this subject our final chapter will be devoted.

CHAPTER VI

On Growing Old

CHILDREN born in 1850 could expect to live, on the average, to the age of forty. Today's babies have a life expectancy of sixty years, and tomorrow's may hope to attain an average of seventy to seventy-five. The noted authority on American vital statistics, Dr. Louis I. Dublin, has shown that this gain in life expectancy applies almost entirely to those under the age of forty. For example, males born in 1901 had a life expectancy of forty-eight years; those born in 1930, of fifty-nine years—a sizable increase. Yet, while in 1901 men forty years old might have expected, on the average, 27¾ additional years of life, in 1930 men of forty could expect only 28½ additional years of life. For women virtually the same is true, although the gain in life expectancy continues for a few more years. The conclusion is inescapable. "The greater part of the gains in the expectation of life at birth may be attributed to the control of infant mortality, to the practical elimination of certain diseases of childhood, and to the curtailment of conditions once considered typical of adolescence and early maturity. Altogether our progress with the diseases of late maturity and old age has not been of any consequence. *To date we have not been able to stretch the life span.*"¹

In considering questions of ageing and death, we must ac-

¹ Dublin, Louis I. *Problems of Ageing*, p. 107. E. V. Cowdry, Ed. Williams & Wilkins, Baltimore, 1939.

cordingly deal with two distinct sets of problems, the one concerned with health and disease, the other with natural senescence, that is, with the wearing out of physiological mechanisms.

UNTIL OUR PRIME, DISEASE AND ACCIDENT ARE THE MAIN
ENEMIES OF LONG LIFE

We owe the great increase in the life expectancy of those *under forty that has been made* during the last century primarily to Louis Pasteur, for *his discovery* that many diseases are due to bacteria opened the way for successful campaigns against those diseases. "Since 1880 . . . typhoid fever and diarrhea and enteritis have diminished almost to the vanishing point in many communities; cholera and typhus fever are rarely causes of death in this country to-day; the incidence and deaths from diphtheria have been greatly reduced; small-pox is under control in all communities where vaccination is practised; bubonic plague, though endemic in certain restricted areas, is not responsible for many cases of disease or many deaths; the infant death rate has been diminished more than 75 per cent.; the death rate from tuberculosis, at one time the most important single cause of death, has been reduced 75 to 80 per cent.; hookworm is controlled in the South; yellow fever is now non-existent in this country; and malaria is under better control."² Approximately 768,000 lives are saved annually among the white population of the United States as a result of the curtailment of the death rate since 1900.

To a great extent the initial achievements in this battle with disease have resulted from the discovery of specific germs and their avenues of infection. Our knowledge of the importance of mosquitoes in transmitting malaria and yellow fever, of

² Horwood, M. P. "An Evaluation of the Factors Responsible for Public Health Progress in the United States." *Science*, Vol. 89, pp. 517-526, June 9, 1939.

flies in spreading the germs of typhoid fever, cholera, dysentery, and other intestinal diseases, and of rats, fleas, and lice in conveying the agents of plague and typhus made rapid advances in the control of these maladies possible. General sanitary measures were taken to prevent the pollution of water and milk supplies, and the screening of houses and warfare on vermin have made the notorious epidemics of past centuries a half-forgotten nightmare. Equally valuable in controlling the inroads of larger parasites have been such discoveries as those that hookworms enter through bare feet and that trichina worms and tapeworms enter by way of half-cooked infected meat.

In another direction progress has also been marked—in the search for ways and means of destroying germs. Outside the body, this was simple. Heat proved a perfect sterilizing agent, making it easy to inaugurate the new day of aseptic surgery. The skin, too, is able to withstand many harsh and effective antiseptics, such as alcohol, carbolic acid, and iodine. On the other hand, it turned out to be considerably more difficult to attack germs once they have gained access to the body, without at the same time harming blood and tissue cells. Here the agent must be chemical, yet nontoxic for us in doses that are toxic for our invaders. Quinine for malaria and Ehrlich's salvarsan for syphilis remained for years the only notable specifics of this character. The recent discoveries of the great value of sulfanilamide, sulfapyridine, sulfathiazole, sulfaguanidine, and sulfadiazine in combating invasions of cocci have given new life to this effort. To be sure, the use of these drugs is not without certain dangers. Nevertheless, the death rate from pneumonia has already been reduced 90 per cent. Blood poisoning, streptococcic sore throat, gonorrhea, meningitis, wound infection, and peritonitis from a ruptured appendix or after abdominal surgery, together with a long list of other infections, are now readily conquered. In addition to these almost magical drugs, new substances are being discovered, some of which offer even more promise than the sulfa

drugs. There are allantoïn, obtained from fly maggots, gramicidin that comes from bacteria in the soil, penicillin, extracted from a common green mold, and several others that may in time become as familiar to us as sulfanilamide is already. These discoveries open a new chapter in the story of man's struggle with the germs of disease.

Diseases spread by the mouth spray of human carriers have also been successfully attacked. Here Pasteur's immunization methods, worked out originally for the bacterial disease anthrax and for virus-produced rabies, have proved to be of most value. Diphtheria, meningitis, infantile paralysis, scarlet fever, measles, and certain types of pneumonia have been conquered through the use of immune serums. A promising new serum for typhus, that scourge of wartime, awaits wholesale testing.³

Another class of diseases has been traced to nutritional deficiencies, and these have proved in the end easiest of all to conquer. Beriberi, scurvy, and pellagra are on their way to join smallpox and "The Black Death" among former scourges of mankind no longer to be feared.

There remains a group of diseases we have been but poorly successful in combating. Some of these are respiratory diseases—influenza, tuberculosis,⁴ the common cold. For these no satisfactory serums have been produced, and as yet no chemical specifics have been found. Others of the group we may term *functional* diseases, since we know very little of their primary causes, other than that they are noninfectious. The most important of these are cancer, diseases of the heart and blood vessels, kidney disorders, the allergies, and insanity. Of all such diseases only diabetes has really been overcome.

³ For more extensive consideration of these subjects, see F. L. Fitzpatrick, *The Control of Organisms*, Chaps. II-VI (Bureau of Publications, Teachers College, Columbia University, New York, 1940).

⁴ Although the death rate from tuberculosis has been reduced 75 to 80 per cent, as quoted above, this disease still ranks seventh among the causes of death in our country.

Cancers and cardiovascular ⁵ and kidney diseases account for nearly one half of all deaths. Colds, allergies, and insanity, although as a rule not fatal, produce temporary or permanent incapacity that in the aggregate means an enormous economic loss.

The great difficulty experienced here is variability. Each of these is not a single disease, but a multitude of diseases, of complex and varied origin. There are at least thirty-two different types of pneumonia; there are many varieties of cancer; there are innumerable allergies; and so on. This is not solely because of the multiplicity of causal agents. By far the greater difficulty arises from constitutional differences. Fortunately for the progress of medicine, we have heretofore been able to ignore such factors in dealing with most diseases—that is, the latter fall into the category of differences due to environment that are manifested in practically all genotypes (category 4, Chapter IV, p. 212). But now, the time has come when we must devote increasing attention to the category of environmentally caused differences that are manifested only in a restricted range of genotypes (category 3). To do this, medical science not only must shift its experimental attack, it must also combat the rather widespread failure of medical men to recognize that the question of constitutional differences has great importance. A medical school that provides any acquaintance with human genetics is still a rare exception, and only recently has the study of heredity even been recommended as a desirable addition to premedical training.

Students of immunity and allergy, and researchers working upon the nature of cancer have been among the first to realize the necessity of dealing with constitutional differences. The importance of these has been impressed upon them by a number of observations such as the following. Gray mice prove more resistant to streptococcus or pneumococcus infection

⁵ The cardiovascular diseases include the chronic heart diseases, angina pectoris, arterial diseases, cerebral hemorrhage, and paralysis unspecified as to cause.

than white mice. Black rats are far more resistant to anthrax than white rats. Susceptibility to specific types of cancer is definitely hereditary in experimental animals. The production of antibodies in similarly inoculated animals may differ enormously. Eskimos and Negroes show a high susceptibility to tuberculosis when living in a temperate climate under civilized conditions. Whites are more susceptible to yellow fever than blacks. Many diseases, long endemic in certain regions and among particular peoples, become epidemic and far more fatal when introduced elsewhere. This appears to be true of measles, smallpox, and syphilis, in addition to the other diseases we have just mentioned. When identical twins have cancer, both have the same type in the same organ at the same age. In general, the same type of tumor affects the various members of a family.

Such evidences of the hereditary basis of susceptibility to disease have been further strengthened by occasional demonstrations of the exact character of the genetic mechanism. Susceptibility to diphtheria has been shown to depend on a simple recessive gene, and the same appears to be true of scarlet fever. The inheritance of resistance and susceptibility to tuberculosis depend on one or two genes only. Common diabetes is due to a simple recessive factor. All allergies, including hay fever, asthma, eczema, hives, and food idiosyncrasies, appear to depend on a single, nonspecific, dominant gene, responsible for the heightened capacity to become sensitized, while the form in which the allergy is manifested is determined partly by exposure and partly by modifying genes. But the irregular type of manifestation that results from hereditary susceptibility plus environmental exposure to a stimulus has been exceedingly difficult to analyze.

These immunities, susceptibilities, and allergies reside partly in the ability, or lack of ability, of the blood or tissues to produce specific antibodies that are carried in the blood; and partly in changes of the cells themselves, changes of which we know little, but which may be thought of as due to the

formation of antibodies that are not liberated.⁶ The capacity to produce antibodies, whether free or unliberated, may be exercised as a normal feature of development; on the other hand, it may remain unexercised until after exposure to the proteins that act as antigens. The antibodies of the blood groups belong in the first category. Susceptibilities and immunities to some diseases are also innate, but in many cases—measles and mumps, for instance—immunity develops only after an attack of the disease. Allergies, cancer, and insanity appear to belong nearly always to the second category. The distinction between these categories is of very great importance. We can do very little to control the conditions of prenatal development, and consequently in the relative constancy of the prenatal environment the genotype is rendered the decisive factor. Thus, as we have seen (p. 95), the blood groups, in the common sense, are inherited. Those traits which mature in the highly variable postnatal environment tend to be decisively affected by it. The final factor in the development of a specific immunity or allergy is commonly exposure to the specific antigen; the final factor in the development of a cancer is commonly chronic irritation; the final factor in the development of manic-depressive insanity is commonly a great emotional strain.

Here then, where we are dealing with *acquired* immunities, allergies, and functional disorders, since the final factor, the environmental one, is decisive, they are nonhereditary in the common sense. Early in the history of immunology, Paul Ehrlich demonstrated this. He showed that, in mice, an acquired immunity to protein poisons could be trans-

⁶ It has been known for a long time that only proteins can act as antigens, that is, as substances which stimulate the production of antibodies. Workers at the Rockefeller Institute in New York have recently demonstrated that the specific character of the antigen-antibody reaction is due to the presence of complex sugars (polysaccharides) attached to the protein molecule. Alone, the sugars have no immunizing effect. Attached to protein molecules, each specific sugar stimulates the production of its specific antibody, regardless of whatever differences may exist in the much greater protein part of the molecule.

mitted maternally but not through the sperm, and that immunity transmitted in this way is evanescent, and cannot be passed on to a second generation. Already in the offspring it is but a *passive* immunity, a mere transmission of the free antibodies themselves from mother to offspring, either after birth by way of the mother's colostrum⁷ or milk, or before birth through the placenta, or perhaps even—though this is doubtful—by way of the egg cytoplasm. In any case, the transfer of free antibodies is to be sharply distinguished from the transmission of genes which lead to the development in the young of their own capacity to form antibodies. The former essentially resembles numerous artificial measures of therapy, such as the hypodermic injection of a dose of the diphtheria antitoxin produced by immunizing horses.

Active immunity, on the other hand, rests upon a genetic basis, whether it is innate or acquired, that is, whether it is a natural feature of development or whether it remains as an undeveloped potentiality until after exposure to certain external factors. Here we can see very clearly how hereditary and environmental factors are inherently involved in producing a trait.

Death from violent accident has in recent years become a very important item in our mortality figures. It now ranks in fifth place as a cause of death, just below influenza and pneumonia (together) and the kidney diseases. Automobile accidents alone kill nearly twice as many people today as does appendicitis. At first we might think that in accidents the environmental factors would always prove decisive. Yet few accidents are wholly external in causation. The constitutional factor is generally of great importance, some people being far more prone to suffer accident than others, and of those who meet equal mishaps some being far more severely injured than others. Heredity, past development, experience, external circumstances, and chance are all inextricably con-

⁷ Colostrum is a watery fluid which precedes by a day or two the secretion of real milk.

cerned in determining the outcome. Let us consider a pertinent example. Each person has characteristic speeds of reaction. Thus the braking reaction important in driving a car takes, on the average, about half a second, measured from a signal given the driver when his foot is on the accelerator to his application of pressure on the brake pedal. The reaction time does not vary with the speed of the car, hence at 60 miles per hour an average driver, perceiving danger, will cover forty-four feet before he can even begin to check his speed. The reaction time of an individual does vary with practice, with age, and with fatigue, but the minimum reaction time is characteristic for each individual. It is inherent, a function of his development, the product of his genes and their environment. Who would doubt that this has a great deal to do with the incidence of automobile accidents? One's fitness to drive a car, then, or more broadly, one's ability to avoid accident in any kind of dangerous situation—these depend on innate factors that we ignore only to our cost.

Should these facts make us fatalistic? That there are hereditary factors of importance among the causes of disease or accident does not mean that we can do nothing to cure or avoid them. On the contrary, to know that an individual's reaction time is important in determining whether or not he is a safe driver should surely enable us to formulate better measures for preventing automobile accidents. People with abnormally slow reaction times ought to be kept out of hazardous occupations. Common diabetes is hereditary, but doses of insulin readily alleviate it. Susceptibility to diphtheria is hereditary, but diphtheria antitoxin is, nonetheless, a potent curative. Why should the knowledge that the tendency to develop cancer may also be hereditary strike terror to our hearts? Actually, the fact that a chemical chain-reaction must lead from the genes to their end-product offers additional points at which the problem may be attacked and brought under control. Let us merely be clear in our minds that, hav-

ing cured an individual's cancer, schizophrenia, or epilepsy, we have not altered any genes that might be concerned, and that these may yet be passed on to a new generation to wreak havoc upon occasion.

Finally, what are the possibilities of further extending our life expectancy in the future? How long, on the average, may we hope to live if there is an appreciable improvement in our control over the cardiovascular and renal diseases, over cancer, tuberculosis, influenza, and pneumonia? About 7.35 years might be gained from the complete elimination of the first two—but, of course, complete elimination is merely hypothetical. The elimination of cancer would add 1.45 years, of tuberculosis 1.1 years, of influenza and pneumonia about 1.4 years. Complete elimination of death from accident would add 1.5 years to the average life span.⁸ While such an achievement must remain theoretical, an average life span of seventy years appears to be attainable in the near future. What this means in terms of the number of survivors and of the increased expectancy at each age is shown in Fig. 107, which also shows the gains made in the United States along these lines in the period between 1901 and 1930.

THE COMPLEX MECHANISMS OF OUR BODIES EVENTUALLY WEAR OUT

We are just beginning to distinguish between ageing and disease, to appreciate that distinction between them made in the last section. The ultimate, the decisive, factor in disease is from without, the action of pathogenic organisms, malnutrition, or excessive strain. On the other hand, *susceptibility* to particular diseases or disorders is a matter of constitutional differences, varying from person to person and altering with age. Thus far, in striving to lengthen the human life span, we have merely learned how to avoid some of the

⁸ Most causes of death affect the two sexes about equally, but males are far more prone to fall victim to accident than females. On the other hand, women are considerably more subject to cancer than men.

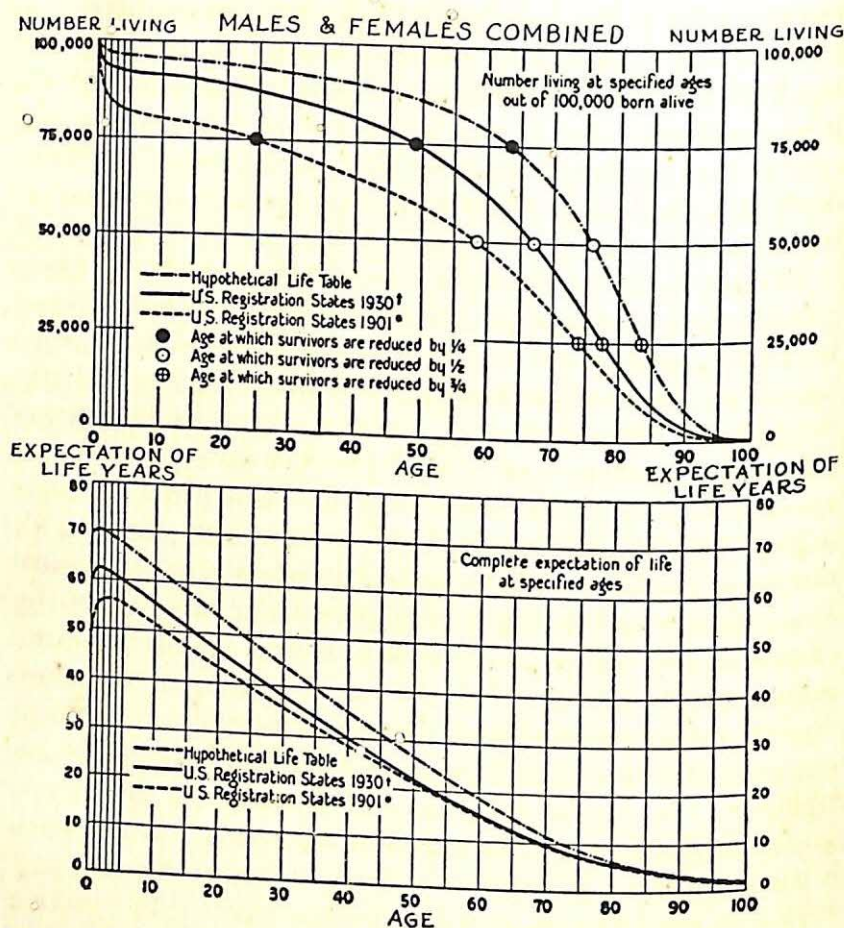


FIG. 107. Comparison of survivors and of expectations of life at specified ages for the United States in 1901, 1930, and in the hypothetical future. (From Dublin and Lotka's *Length of Life*. Courtesy of Ronald Press Co.)

external factors that accelerate ageing. We have made no progress in learning how to slow down the inherent ageing process itself. What has really been discovered about the latter?

It is evident, to start with, that each animal species has its own characteristic life span. A rat is ancient at three years, a horse at thirty, a man at one hundred, a Galapagos tortoise

not until about five hundred. We are more immediately interested in the variability within a species, to be sure, and would like to know to what extent that is fixed and how far it is modifiable. Yet, if we can gain some inkling why one species lives on the average two years and another two hundred, that would very likely throw considerable light also on the nature of intraspecific variability in the life span.

The life span must obviously be correlated with the other physiological processes that are characteristic for each species. It cannot stand apart. It but marks the duration of that unbroken sequence of physiological and structural changes taking place in every organism, of which early growth and development comprise but a segment. "We must all be born again atom by atom from hour to hour, or perish all at once beyond repair," said Holmes. Numerous recent studies with nutrients made artificially radioactive bear out his words. Even the bones and teeth, most permanent of all the parts of our bodies, are in constant flux. Could ageing fail to be determined by the nature of the earlier processes? The more rapidly growth and differentiation occur, the sooner must maturity be attained, and the earlier will senescence encroach upon it. The slower one lives and changes, the slower one grows—and the longer one may hope to live. A dormant seed, a bacterial spore, an encysted animal—these may live for centuries, it would seem. Small organisms vitrified by extreme cold and refrigerated appear to be potentially immortal. Or life may be prolonged by reversing the direction of growth. It is a fairly common experiment in biological laboratories to make planarian flatworms "grow younger" simply by starving them, for this brings about a decrease in their size and dedifferentiation of their tissues, processes which feeding will again reverse at any time. Cantaloupe seedlings that are germinated on agar, without any nutrients whatever, at first grow vigorously, then remain in suspended animation for a while, and thereafter gradually die. There is a high degree of negative correlation between their rates of growth during the

growing period and the total duration of their lives (—5 or —.6). The faster they grow, the sooner they die. Also, the faster they grow, the higher their expenditure of energy, their rate of metabolism. With rats it is the same. When retarded in growth by being kept on a maintenance diet, they still appear young at an age of 700 or even 1,000 days, while those that grow up normally are already aged or dead. When returned to a diet adequate for growth, the stunted rats will grow at a normal rate and mature in nearly normal fashion, except that they seem unable to attain quite the usual size. Evidently organisms grow old fastest while they are living most intensely and developing most rapidly.

The relation between the basal rate of metabolism and the life span is also to be found in comparing the two sexes. The difference between the metabolic rates of males and females is negatively correlated with their duration of life. This is true for water fleas (*Daphnia*); it is true for man; presumably it is a general phenomenon.

One school of biologists holds that these facts are indicative of an inherent ageing process in the life-substance itself. Protoplasm is a very unstable union of proteins and lipoids, they say, an elaborate colloidal system easily destroyed by whatever chemical and physical agents act on proteins or lipoids. Such colloids appear to lose their power to adsorb as they grow older. Their capacity to take up water also diminishes and they shrink irreversibly. Gradually they lose their stability and become less reactive—and this is the basis of senescence. Destroy the dispersion medium of the colloidal system, disrupt the unstable protein-lipoid compounds, coagulate or dissolve out essential materials—metabolism will be paralyzed, and death supervene.

This conception serves to explain why we shrink in weight and decline in stature as we become elderly—our colloids are losing their capacity to bind water. It also makes clear why younger individuals metabolize at a higher rate per unit of body weight, since their colloids possess maximum reactivity.

It explains why poikilothermic⁹ animals have a life span which varies inversely with temperature, for it can be shown that colloids age more rapidly as temperature goes up. Maybe the often fatal hardening of our arteries is due to the loss of resiliency and flexibility on the part of the colloids that make up the elastic tissue of the walls of the blood vessels. Perhaps this is why the old adapt themselves less quickly and effectively than do younger people to virtually all changes, both internal and external, with "a curious kind of faltering or indecision in regulation. . . . The homeostatic mechanisms become more and more restricted in their ability to maintain the essential stability of the blood."¹⁰

Other biologists feel that this concept of ageing and death is probably too simple. Certainly our investigations have not gone far enough to prove the causal relation of changes in the body colloids to any of the characteristics of ageing. The theory also appears to ignore the potential immortality of relatively undifferentiated cells. Among unicellular animals, some strains are able to continue living and reproducing indefinitely, even without recourse to that process of endomixis whereby other strains replace their macronucleus by a fresh one from a reserve store, the micronucleus. In the former, favored genotypes, the hourly repair of the protoplasm and the elimination of wastes are apparently in balance with the destructive forces, and no drastic regeneration or rejuvenescence is necessary. To be sure, strains of other genetic constitutions are less well balanced. Some of these tend to degenerate, and will die out except for the renovation of endomixis. For others not even this suffices—from their origin they are doomed to inevitable extinction, even in the most favorable of environments. Do not facts such as these mean that ageing and death result from the failure of repair and elimination to keep pace with exhaustion, dissolution, and

⁹ Poikilothermic organisms are those without the capacity to regulate their body temperature. Their rate of metabolism consequently varies with the temperature of their external surroundings.

¹⁰ Cowdry, E. V. "We Grow Old." *Scientific Monthly*, Vol. 50, p. 53, 1940.

the accumulation of wastes? Many think so, and point to the experimental work of Alexis Carrel, Lecomte du Nouÿ, and others as additional proof.

Carrel was the first to develop successful methods for continuously culturing the tissues of higher animals *in vitro*. He did this by growing the cells in a mixture of embryonic juice and blood plasma that was carefully controlled to prevent bacterial infection and to maintain favorable conditions, and by then transferring a portion of the tissue to fresh fluid every two or three days. Growth of the tissues by cell division is kept up at a stupendous rate. They double about every two days, as long as their nutritive medium is kept fresh. If, however, they are not transferred, death will occur in a very few days, as the cells in the interior of the growing mass are increasingly cut off from food and air, and their wastes are excreted but slowly through the surrounding cells. Toxic substances accumulate and upon the death of cells in the interior are released, poisoning the others. Carrel was led from these observations to study what effect the age of the animals from which the plasma was taken would have upon the growth of cells in tissue-cultures. He found that the older the animal from which the supply came, the shorter the time cultured cells would survive in it. Evidently, with age blood undergoes some form of chemical change that tends to inhibit growth and cell division, and to put a term to life. For a variety of birds and mammals, including man, there is a logarithmic inverse proportionality between increasing duration of life and declining rate of growth (Fig. 108A).

This helped to explain one of Carrel's earlier experiments. A decrepit dog, nearly eighteen years old, had been anesthetized and bled. Nearly two thirds of his blood was removed, the red cells were centrifuged out, washed, recentrifuged, mixed with fresh Ringer's solution to restore the original volume, and then reinjected into the dog. After he began to recover from the shock of the operation, the procedure was repeated a second time. The almost complete replacement

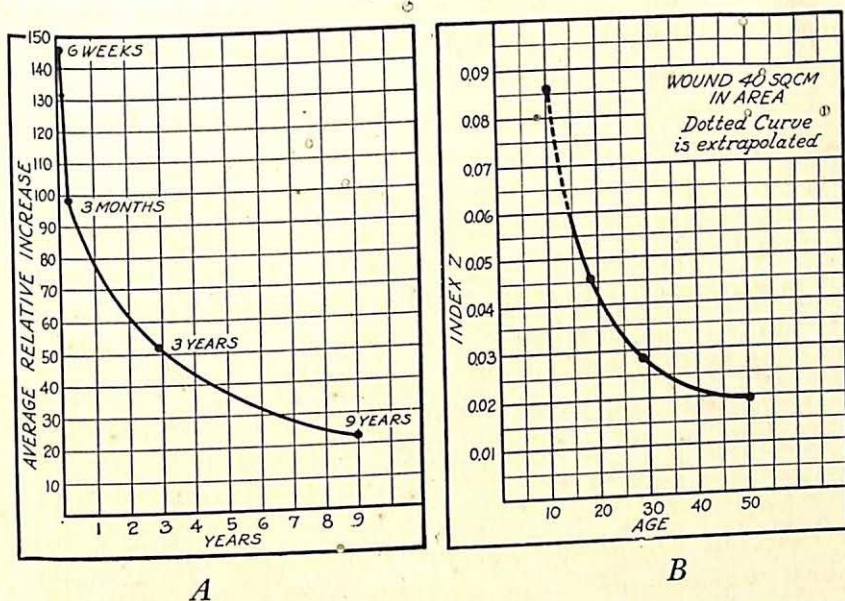


FIG. 108. *A*, the relation between the age of animals from which serum was taken and the rate of growth of cells (fibroblasts) cultured in that serum. *B*, the relation between the age of a patient and the rate of healing of his wounds (cicatriziation). (Redrawn from du Noüy's *Biological Time*. Courtesy of The Macmillan Company)

of the blood plasma of the aged dog by fresh Ringer's solution had the most startling results. The dog's appetite improved, "he ran and barked, a thing he had not done for years. His eyes were clear, his eyelids normal. His coat started to come in; he was gay, active, and most important of all, he was no longer indifferent to the charms of the other sex."¹¹ He was rejuvenated.

Lecomte du Noüy, of the Pasteur Institute, made studies during the World War of 1914-18 that indicate a parallel decrease with age in the rapidity with which wounds of a given area heal over (Fig. 108*B*). It is possible to predict with great accuracy, for a man of any given age, how long it

¹¹ Lecomte du Noüy, P. *Biological Time*, p. 115. Macmillan, New York, 1937. This book also reports the experimental work mentioned here.

will take a clean, noninfected wound of a certain area to heal.

Studies like these have led a number of biologists to the concept of physiological time—time measured not by the revolutions of the earth around the sun or its rotation on its axis, but by the very changes within each organism itself. Since these changes do not proceed uniformly, since the rate of growing and living declines as age increases, a sidereal year represents very different relative values in this biological time at different absolute ages. It appears that the value of a year at any age is about equal to its proportion of the total life up to that age, so that a year to a child of ten has approximately four times the value of a year to a person of forty, and six times the value of a year to a person of sixty. To put it another way, time seems to flow more slowly to the young. Each of us can readily recollect the seemingly interminable way a year stretched from one Christmas to the next when we were seven. Endless hours filled each of those childhood days; swiftly they speed past us now. These experiments show that our memory has not played us false. Our sense of time is not based on clocks or stars or even the alternation of day and night, but on the changes within us as we grow and develop.

But growth and differentiation do not proceed uniformly for the body as a whole, as we have seen, and neither does ageing. The thymus gland begins to decline at puberty. So do the tonsils and other lymphoid tissues, the tonsils usually becoming senile by the time we are fifty or sixty years of age. The reproductive organs cease activity at menopause in women; and the prostate gland of males, an important factor in their sexual activity, is old at sixty. Bones and cartilage suffer from a progressive loss of mineral content, and become more brittle. There is on the whole less tooth decay, but the gums recede and teeth are more fully exposed and tend to be lost. Muscles acquire a proportionally greater amount of connective tissue. The skin atrophies, and folds and wrinkles appear as its elastic tissue degenerates and the subcutaneous fat de-

posits are withdrawn. The hair grays and falls out. The nails, especially the toenails, tend to thicken and become deformed as their rate of growth slows down. Hearing for tones above high C becomes impaired. Even within a single organ there may be differences in the ageing process. In the brain, for instance, white matter suffers more than the gray, and the frontal regions more than the more primitive parts of the brain.

These are nonvital functions. The heart and blood vessels are usually first of the vital systems to succumb—there is thus a reasonably sound basis for the saying that “a man is as old as his arteries.” On the other hand, some systems show little or no sign of decline. It has been said on good authority that “the possible length of useful life of the visual apparatus is at least 120 to 130 years,”¹² that the digestive system too is good for more than three score years and ten.

We should not overlook the fact that the rates of ageing of many organs and systems are interdependent. The endocrine glands exert a potent influence over other systems in this respect. Perhaps the brain and nervous system would function indefinitely were it not for the failure of their blood vessels. Whether the kidneys might last longer than they do, if their elaborate circulation only held good, cannot be said. Perhaps the nurture of isolated organs in the Carrel and Lindbergh artificial heart system will answer some of these questions, but within the body we must continue to think in terms of interrelationships.

Recently Dr. Henry S. Simms, of Columbia University, has made an important study which indicates that both the increasing debility and the increasing death rate that are manifestations of senescence are the result of the same general physiological alterations. More than a century ago, Gompertz declared that after the age of thirty-five the probability of death increases with increasing age in geometrical progres-

¹² Cowdry, E. V. “We Grow Old.” *Scientific Monthly*, Vol. 50, p. 52, 1940.

sion, like accumulating compound interest.¹³ Dr. Simms has calculated from the total deaths from all causes reported for the year 1936 that the probability of death increases regularly 8.1 per cent per year. The feature of most interest in his calculations is that nearly all diseases fall into two clear-cut groups, each of which obeys the compound interest law, but at different rates. The probability of death from each of the cardiovascular and kidney diseases increases about 11 per cent per year. The other group, in which the probability of death increases about 5 per cent per year, includes most infectious diseases, digestive diseases, lobar pneumonia, diseases of the nervous system which are not vascular in character, respiratory diseases (except tuberculosis and bronchopneumonia), goiter, pellagra, arthritis, and diseases of the skin and bones—surely an extraordinary assemblage of human ailments. Yet since the probability of death increases with age similarly for each member of this group, their lethality in all probability depends on some common physiological condition (Q) which alters with age. What this may be we have at present no inkling, but it is something to have learned that death from so wide a variety of causes may be due to a single constitutional factor.

For the cardiovascular and renal diseases, much the same may be said. Here an additional constitutional factor (R), perhaps the elasticity of the arteries or the permeability of the capillaries, is involved. If the Q factor is concerned here too, as seems probable, the R factor must alter at the rate of 6 per cent per year. The probability of death from a few other diseases, such as cancer and bronchopneumonia, also increases with age, but irregularly, not as compound interest. Even the increase in senile debility would appear to follow the law. "The high death rate in old age is the result of changes which make us succumb more readily to all diseases, although the

¹³ $P_t = P_0 \cdot e^{kt}$, where P_t is the probability of death at a given time, t , and P_0 is the probability of death at birth, e is the logarithmic base, and k is a positive constant (the "interest rate").

change is faster for the vascular diseases. Nearly four deaths out of five after the age of thirty are due not to a greater prevalence of disease but rather to the change in the *Q* and *R* functions which increases the death-rate from the same diseases which affect young people."¹⁴

How much more hopeful is such a situation than would be the random accumulation of degenerative changes. To have one major enemy or two, to seek them out, combat them, and overcome them singly—this science has often done. We may yet live to see it done again. But who can fight a mist, a creeping miasma?

Whatever such constitutional factors may be, however modifiable by environmental circumstance, there is little doubt that the genes have much to say in determining them. Studies by Karl Pearson in England and by Raymond Pearl in the United States indicate that longevity in man is definitely influenced by hereditary factors. Pearl, for instance, found in the study he made that almost 87 per cent of those who lived to a very old age (over ninety) had at least one long-lived parent (over seventy), and about an equal proportion had at least two long-lived grandparents. Any conclusion as to the degree of importance of heredity here must be accepted with due reserve. We should be well aware that not only may positive correlations of this type arise from resemblances in genotype but that correspondences in environment will also tend to produce them. Thus mortality rates vary significantly with income level and hazard of occupation, and the death rate among infants of the poor is far greater than that among infants of the well-to-do. The potency of hereditary factors in determining longevity must accordingly be assessed differently in each of the innumerable varieties of

¹⁴ Simms, Henry S. "Physiological Alterations as the Cause of Senile Debility and Senile Mortality." *Science*, Vol. 91 ns., pp. 7-9, January 5, 1940. A 1941 report that the presence of the adreno-cortical hormones in the heart tissues is necessary for the normal functioning of the heart and that either too much or too little of these over a prolonged period will lead to heart failure may possibly be a clue to the nature of the *R* function.

circumstance. Pearl performed a series of experiments with inbred wild-type and vestigial-winged *Drosophila* that makes the situation clear. Vestigial-winged flies, when raised under standard laboratory conditions, have a higher mortality rate than flies with normal wings. Their duration of life was, on the average, less than half that of the strain of wild flies used. However, by increasing the density of the wild-type flies per bottle, their life curve could be made to correspond to that of vestigial flies; while, under complete starvation, the vestigial flies equaled the performance of the normal flies, regardless of the initial density. Clearly, the hereditary factor that differentiates vestigial from wild type does not inherently determine the length of life. It somehow militates against an optimum use of the standard environment by the vestigial-winged type. Other experiments have shown that wild populations contain numerous genetic factors which similarly vary the adaptation to particular environments. Heredity and environment must always be considered together.¹⁵

In most cases the influence of the genes is not negligible. What an abundance of lethal and semilethal genes are known in those organisms which have been studied genetically! Most of those in man produce fatal consequences in early development, but there are a number which act later. The dominant gene for Huntington's chorea usually manifests no effects until after the carrier has attained maturity, and often not until the age of thirty-five or forty. Diabetes is commonly not manifested until middle age. Hemophilia is sometimes not fatal until the victim is well on in life. The tendency to develop cancer finds expression, as a rule, only in late maturity or old age. Just as plausibly we may assume that there are also genes which, either singly or in conjunction, are responsible for the breakdown of the circulatory system or kidneys.

¹⁵ Pearl, Raymond and Pearl, Ruth D. *The Ancestry of the Long-Lived*. Johns Hopkins Press, Baltimore, 1934.

Pearl, Raymond. "Experiments on Longevity." *Quarterly Review of Biology*, Vol. 3, pp. 391-407, 1928.

On these questions research into the causes of death of identical twins, particularly those who have lived apart for some time prior to death, should be highly illuminating. There are general reports that identical twins frequently fall ill of the same diseases and die within weeks or days of each other, but no extensive study has as yet been undertaken. Most studies of twins stop short with their history at the time of investigation—or at least the twins under observation were initially so young that follow-up studies have not yet reached the period of their old age and death.

Some day men may live to the average age of a century. First, however, there will have to be an intensive search for the genes that make for long life and a laborious exploration of the ways in which they produce their effects. Working from the environmental side, we may improve our measures to ward off disease and accident and to strengthen our resistance to whatever factors speed up the impairment of our vital faculties. But some day we may reach this goal, perhaps even in our children's time. Will men be any happier then than we are today? If a lengthened life means merely a prolongation of the years of senility and decrepitude, who could wish for it? Or is a placid, vegetative existence of a century to be prized more highly than a short life and a merry one?

These are questions of values, and men will judge variously. There were Schubert and Keats who matured early but died young. There were also Titian and Edison, who did some of their best work after they were seventy, men who grew greater as they grew wiser in experience, yet remained eager as youths to learn something new and to accomplish something finer. If most old people lose their terror of death as their passions decline and their sensibility to pain diminishes, whence so startling a zest for life in others? Does it come from their continuing purpose in existence? If so, how important for us to plan for our future years—not so much for our security as for the continuation of useful activities, of vital interests. To keep on growing—

is this our fountain of youth? Our bodies have differentiated until with specialization they have lost the capacity to grow and even to repair anything more than minor injuries. The mind, however, may hold its power to develop, insofar as we know, as long as it is fed and exercised.

Genes alone do not make the man, and our development, as it progresses, tends to become more modifiable by environmental factors. For this reason, as we age we need to devote a greater proportion of our energy to conscious direction of, and control over, the changes within us, lest we suffer the dire consequences of haphazard development. Our greatest opportunity to do this undoubtedly lies in the sphere of the mind.

The peril for us lies in the probability that in becoming overspecialized for a particular niche in human society we may, like our cells and tissues, lose our adaptability. How many men, as they retire or are thrust out from lifelong occupations, are at a loss what to do with themselves! Yet the mind need never be narrowed to occupational interests alone. One's occupation should rather be the center of an ever broadening sphere of related interests, and one's life, as Havelock Ellis urged in *The Dance of Life*, an art—the greatest, indeed, of all the arts—consciously pursued as such, to its very end. The world has need of old people, need for their wisdom, their guidance, and their experience. But for that day when we too shall be old we must plan and prepare now, lest our wisdom and skill be found inadequate.

In the end we shall pass away—as “the grass withereth and the flower fadeth.” Only those genes that made us, as they made our forefathers, cast into ever new combinations in the recurrent cycle of sexual reproduction, may live on to produce new hands, new eyes, and new minds, to test out each variety of environment, to continue our struggle to mold a world one step nearer the heart's desire.



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